Guidelines for the management of acute pain in emergency situations

2025 Update

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Author contributions

All authors had access to all data and evidential materials and take responsibility for the integrity of the guideline and the accuracy of analyses. All authors were involved in the concept and design of the guidelines, drafting the guideline handbook and critical revision of all drafts.

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Foreword: EUSEM President

The management of acute pain in emergency and pre-hospital settings stands at a pivotal crossroads. Over the past five years, the landscape has evolved rapidly, propelled by the opioid crisis, advances in pharmacological and non-pharmacological therapies, and the increasing integration of technology in clinical practice. The imperative for safer, more effective, and equitable pain control has never been clearer—or more pressing.

Pain remains the leading reason for emergency medical attendance across Europe and globally. Yet, despite its prevalence and the well-documented harm of both under- and over-treatment, practice remains inconsistent. Historical reliance on opioids for moderate-to-severe pain has contributed to the rise of opioid misuse and adverse events, underscoring the urgent need for stewardship and alternative approaches. The COVID-19 pandemic further challenged our systems, highlighting gaps in pain assessment, disparities in care, and the critical importance of flexibility and innovation.

These new guidelines synthesise the latest evidence and best practice, reflecting a multimodal, mechanism-based approach to pain relief from prioritised pain assessment through to effective pain relief, tailored to the needs of vulnerable groups for the benefit of all our patients.

Assessment is prioritised as the foundation of effective pain management. Guidelines call for systematic, repeated pain evaluations beginning at first contact through to discharge, using validated tools and recognising the deeply subjective nature of pain. Regular audit cycles and ongoing professional education are highlighted as critical drivers of quality, equity, and patient-centred outcomes. Recommendations from the World Health Organization based on foundation of the CERTA (Channels-Enzymes-Receptors Targeted Analgesia) principles and the modified acute pain management framework anchors pharmacological choices to pathophysiology, advocating the use of non-opioid agents wherever feasible.

The recommendations presented here are both pragmatic and ambitious, striving for a future where acute pain management is personalised, balanced, and evidence-based. By shifting cultural expectations, embedding stewardship, and embracing technological advances, we can close the enduring gap between evidence and everyday practice.

I want to thank the excellent European Pain Initiative committee who conducted this work, ably led by Professor Saïd Hachimi-Idrissi and supported by colleagues from across Europe. With these guidelines, we invite all clinicians, educators, and system leaders to join us in redefining the standard for acute pain management across emergency and pre-hospital care.

Dr Robert Leach
President of EUSEM

Preface

This updated handbook is designed to improve the assessment and management of acute pain in emergency and pre-hospital settings across Europe. Developed under the auspices of EUSEM and the European Pain Initiative, it offers practical, evidence-based strategies tailored for first responders, paramedics, and emergency physicians.

Since our 2020 edition, the pain management landscape has evolved significantly, driven by the opioid crisis, advances in multimodal therapies, and the growing role of technology in clinical decision-making. Pain remains the most common reason for emergency attendance, yet its treatment is still inconsistent. These guidelines aim to address that gap with updated, safer, and more individualised approaches.

New in this edition is a refined alignment with the WHO framework. It encourages judicious opioid use, promotes non-opioid strategies, and emphasises repeated, structured pain assessment using validated tools. Special attention is given to vulnerable groups such as children, the elderly, and patients with cognitive or substance use disorders.

The handbook retains essential content from the previous edition, including pain physiology and assessment methods, and now includes updated clinical algorithms, decision aids, and guidance on integrating point-of-care technology.

Our goal is to promote more consistent, compassionate, and effective pain care rooted in evidence, equity, and clinical excellence.

On behalf of the European Pain Initiative, I extend my sincere thanks to the dedicated committee members and EUSEM colleagues who contributed to this important work.

Special thanks also to Aguettant for their unrestricted grant, which supported the development of this handbook.

Professor Saïd Hachimi-Idrissi
University of Ghent, Belgium

Development of the updated recommendations for acute pain management in the emergency setting: process

These updated guidelines were achieved through a thorough expert review of the current handbook and a comprehensive systematic literature review based on strategic methodology.[1,2] Relevant publications were identified via a literature search performed using MEDLINE, Cochrane database, Google Scholar and EMBASE online databases on 25th June 2025. All experts determined a search strategy that included both free-text words and medical subject headings (MeSH) and search parameters can be found in **Table 1**. Search parameters were limited to material published from January 2020 to May 2025. English-language articles published since 2020 returned from the search were considered against a series of agreed inclusion and exclusion criteria (**Table 2**) and levels of evidence for pharmacological and non-pharmacological pain management methods were ascribed to assist in determining management recommendations (**Table 3**). From 1,089 identified articles, and a first-pass screen to 326, a final screen determined the inclusion of 100 articles. Where required, there have been further inclusions of older literature sources as some analgesics in the emergency setting were first made available many years ago and newer literature does not exist. During the development of the handbook, additional articles were uncovered and, with committee discussion, were included or discarded.

The systematic literature review has been conducted in line with the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines (**Figure 1**).[2]

First pass evaluation was undertaken by Said Hachimi-Idrissi and a medical writer reviewing titles and abstracts against agreed inclusion and exclusion criteria (**Table 2**). There was a second-pass evaluation of published full texts to determine which met eligibility criteria for subsequent review and discussion by all experts. All experts independently reviewed potentially relevant studies to determine their eligibility and the strength of the evidence. Any disagreements were resolved through expert discussion in online face-to-face meetings. A working document package was generated for further review with additional publications included from outside the strict definitions applied in the search strategy as suggested by the experts, for example including artificial intelligence publications with relevance to ED/prehospital settings, and this package of evidence was reviewed against bias criteria according to GRADE criteria (**Table 3**). The original literature identified in 2019 was similarly subjected to a renewed review of bias so that all data used in this handbook has been subjected to an identical process. For more details of the literature regarding the pharmacological management of acute pain see the Supplementary material to **Chapter 5**. Similarly, literature exploring the non-pharmacological management of pain can be accessed in **Chapter 3**.

Once all data were identified, online face-to-face meetings of all experts were convened to discuss the identified data, explore additional data for inclusion and determine recommendations for management of acute pain in emergency settings. All expert views were incorporated and only once a majority consensus (80%) of all involved experts was achieved, were recommendations considered consensus.

Table 1. Literature search parameters from 1st January 2020 to 30th May 2025

Database	Search
PubMed/Embase/ Cochrane Limits: none Methodologic filter: none	“Emergency medicine” OR “Emergency nursing” OR “Emergency medical services” OR “Emergency room” OR Emergency department” OR Pre-hospital OR prehospital AND pain AND analges*
	((“Emergency department” OR Pre-hospital OR prehospital AND pain AND analges*) AND (intravenous[Title/Abstract]))
	((“Emergency department” OR Pre-hospital OR prehospital AND pain AND analges*) AND (intranasal[Title/Abstract]))
	“Emergency department” OR Pre-hospital OR prehospital AND pain AND analges*
	“Emergency medicine” OR Pre-hospital OR prehospital AND pain AND ibuprofen
	“Emergency medicine” OR Pre-hospital OR prehospital AND pain AND paracetamol
	“Emergency medicine” OR Pre-hospital OR prehospital AND pain AND NSAIDs
	“Emergency medicine” OR Pre-hospital OR prehospital AND pain AND metamizole
	“Emergency medicine” OR Pre-hospital OR prehospital AND pain AND nitrous oxide
	“Emergency medicine” OR Pre-hospital OR prehospital AND pain AND methoxyflurane
	“Emergency medicine” OR Pre-hospital OR prehospital AND pain AND fentanyl
	“Emergency medicine” OR Pre-hospital OR prehospital AND pain AND morphine
	“Emergency medicine” OR Pre-hospital OR prehospital AND pain AND opioids
	“Emergency medicine” OR Pre-hospital OR prehospital AND pain AND opioids OR fentanyl OR morphine
	“Emergency medicine” OR Pre-hospital OR prehospital AND pain AND ketamine
	“Emergency medicine” OR “Emergency nursing” OR “Emergency medical services” OR Pre-hospital OR prehospital AND pain AND analges*
	“Acute pain” AND Analges* AND wound* OR injur* AND “pain therapy” AND Pre-hospital OR prehospital AND “Emergency medicine” OR “Emergency nursing” OR “Emergency medical services”
	“pre-hospital” OR prehospital AND pain AND analges*
	“pre-hospital” OR prehospital AND pain
	Analges* OR “therapy” AND “acute pain” OR pain AND “pre-hospital” OR prehospital
	Analges* OR “therapy” AND “acute pain” AND “pre-hospital” OR prehospital
	Analges* OR “therapy” AND “acute pain” AND emergency OR “pre-hospital” OR prehospital
	Analges* OR “therapy” AND “acute pain” AND emergency OR “pre-hospital”
	Analges* OR “therapy” AND “acute pain” AND “intravenous” OR “intranasal” OR “inhaled” OR “intramuscular”
	Analges* OR “therapy” AND “acute pain”
	Analges* AND “acute pain”

Table 2. Inclusion and exclusion criteria for reviewed data

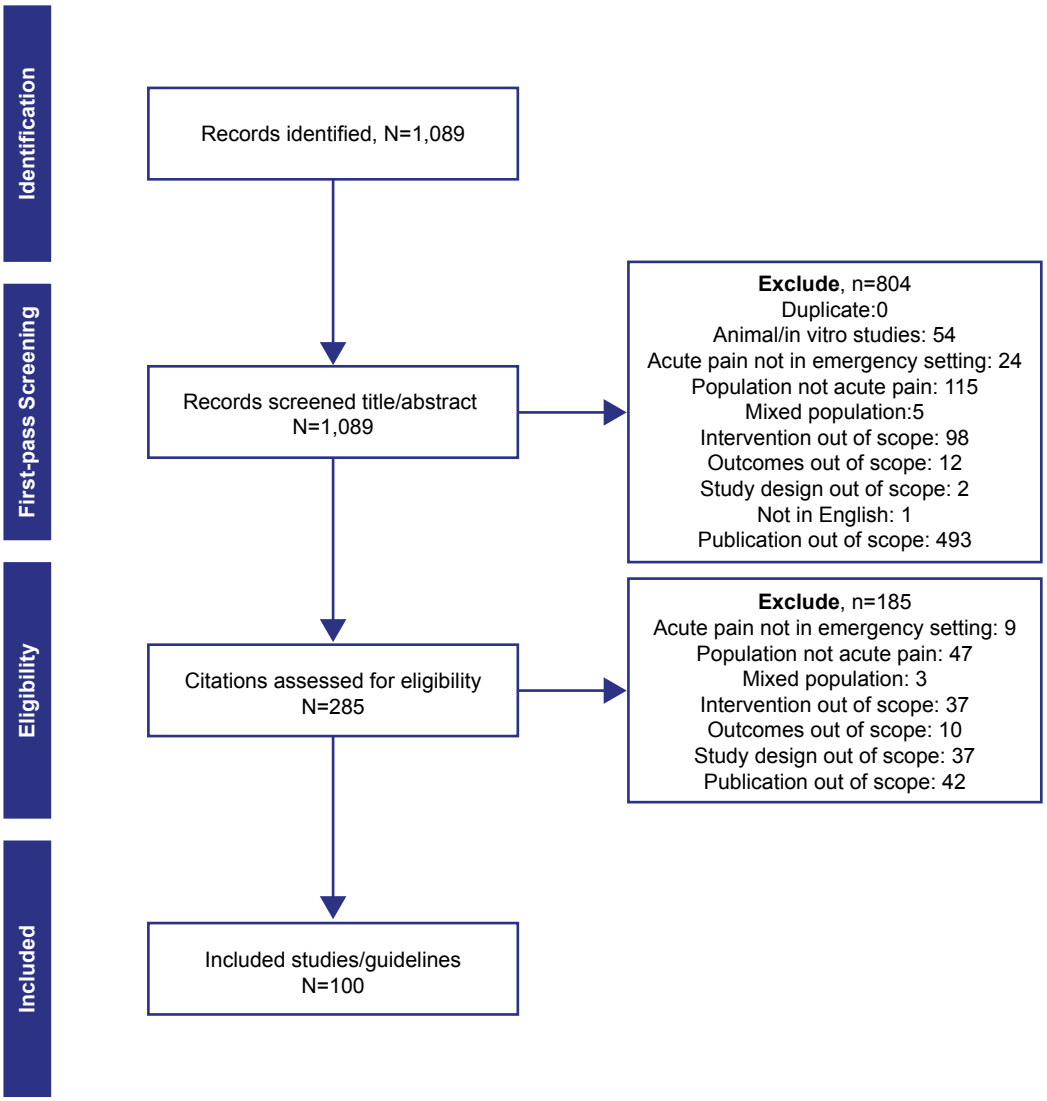
Inclusion	Exclusion
RCTs	Individual case reports
Clinical trials without randomisation e.g. open label, observational, retrospective	Treatment methods not found in the ED e.g. acupuncture
Meta analyses	After 30 May 2025
Case series/case-controlled studies	Publication not in English
Systematic reviews	
English language	

RCTs, randomised clinical trials

Table 3. GRADE approach adopted for evidence reviewed for bias and graded accordingly.[3]

IA	Evidence from meta-analysis of randomised controlled trials with a very low risk of bias
IB	Evidence from at least one randomised controlled trial with a low risk of bias
1C	Evidence from meta-analysis of randomised controlled trials with a high risk of bias
IIA	Evidence from at least one controlled study without randomisation with low risk of confounding bias and high probability that the relationship is causal
IIB	Evidence from at least one other type of quasi-experimental study with low risk of confounding or bias and a moderate probability that the relationship is causal
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies high risk for potential bias or confounding and a risk that the relationship identified is not causal
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Figure 1. PRISMA: overview of literature used to construct EUSEM recommendations



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GUIDELINES FOR THE MANAGEMENT OF ACUTE PAIN IN EMERGENCY SITUATIONS

The content of this chapter remains consistent to that developed in 2020

CHAPTER 1:

The current state of acute pain management in emergency situations in Europe

Prevalence of acute pain in emergency situations

Pain is defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'[1] Acute pain is typically of sudden onset and of limited duration and is provoked by a specific injury or disease.[2] It is highly prevalent, with up to 70% of patients in the pre-hospital setting[3,4] and between 60% and 90% of patients entering the Emergency Department (ED) reporting pain.[5-7] Pain is a primary complaint in half of all ED visits.[6] Extrapolating the prevalence of acute pain to the national scale using available data from Europe on the annual number of ED visits suggests that millions of people in Europe suffer from acute pain every year,[8-11] making its management a massive undertaking and of great importance.

This chapter provides an overview of the current situation in Europe as regards the unmet needs and current practice in the management of acute pain in the pre-hospital and ED settings, and outlines the guidelines that are available to advise emergency medicine professionals.

Oligoanalgesia in emergency settings: pre-hospital

Acute pain is often poorly assessed and inadequately treated in the pre-hospital setting.[4,12-17] Initial and final assessment of pain does not take place in one-third to almost one-half of cases, and when pain assessment does take place, many patients reporting moderate to severe pain do not receive analgesia.[14] In an Australian study of 333 patients aged over 65 years attended to by an ambulance following a fall resulting in suspected bone fracture, initial and final pain assessment was undertaken at the scene in around half of cases, and only 60% of all patients with suspected fracture received analgesia.[14] Similarly, a retrospective chart review of 1,407 ambulance patients in the Netherlands found that while 70% of patients reported pain, only 31% had a systematic pain assessment and only 42% received analgesia.[3]

Oligoanalgesia may result from a lack of availability of analgesics to pre-hospital personnel. A study in Italy reported that 12% of all ambulances do not carry strong analgesics such as opioids, and 10% of all ambulances carry no analgesic medication at all, despite 42% of patients reporting moderate to unbearable pain.[12] In Switzerland, a ten-year retrospective review of 1,202 patients attended by air ambulance found oligoanalgesia in 43% of cases.[18] In this study, predictors of undertreated pain included male gender, pain score NRS > 4, no analgesia and lack of experience of the attending physician. Oligoanalgesia was due to insufficient analgesic dosing in 75% of cases and a complete lack of analgesia administration in 25%.[18] In contrast, a study in France showed that 90% of paediatric patients who reported pain received analgesia while being transported by mobile intensive care units (MICU). It was

noted that this unusually high figure may be related to the fact that the medical team on board the MICU included a trained ambulance driver, an emergency physician, a nurse anaesthetist, and sometimes a medical student, compared with other countries where ambulances are generally staffed by paramedics or ambulance staff.[19]

Oligoanalgesia in emergency settings: ED

In addition to the issues seen in pre-hospital emergency analgesia, there are unmet needs associated with acute pain management in the ED setting. The problem of oligoanalgesia in the ED was first acknowledged in the late 1980s.[20] Since then, a considerable number of studies have shown that pain is assessed in some, but by no means all, patients and that even when pain is assessed and documented many patients do not receive analgesia.[21,22] In a prospective study carried out in a Norwegian university hospital ED in 2015, 77% of 764 patients were evaluated for pain on arrival, and of those with moderate to severe pain, only 14% were given analgesics.[21] In a prospective, observational study of 2,838 patients visiting an urban ED in Italy, 71% presented with pain, but only one-third (32%) received pharmacological pain relief.[23] Of these, 76% rated their pain as severe and 19% as moderate.[23] Pain may also persist after the patient has left the ED. Of 582 consecutive patients presenting at an ED with pain, 37% of patients had ongoing pain a week after discharge, despite being prescribed analgesic therapy.[24]

Barriers to effective pain management in the ED are varied and include poor assessment of pain, limited availability of opioids, resistance among healthcare providers to prescribe opioids, fear of opioid dependence or potential for diversion and abuse, failure to follow pain management guidelines, overcrowding in the ED and lack of pain management knowledge or resources.[12,13,22,24-29]

Oligoanalgesia in the ED can affect any patient, but is a particularly well-recognised issue in paediatric patients.[30] Pain assessment can be more difficult to perform in children,[30] and this group is often more challenging to manage than adults, for reasons such as heightened anxiety and difficulties in obtaining intravenous (IV) access.[28,31] Even when pain scores are documented, only two-thirds of children in pain in the ED may receive analgesia.[32]

Current practice in analgesia in emergency situations

No single standard of care (SoC) currently exists for the treatment of pain in an emergency situation. The choice of analgesic depends on severity of pain, nature of injury and local protocols. In general, those with mild pain tend to receive paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), those with moderate pain receive paracetamol, NSAIDs, nitrous oxide or weak opioids, while IV morphine or ketamine are reserved for those with severe pain.[33-35] Paracetamol and NSAIDs are more common in the ED setting than the pre-hospital setting; ketamine is mainly used in the pre-hospital setting and nitrous oxide and opioids are used in both.[28]

A range of personnel may be involved in the care of a patient with acute pain in an emergency situation, including emergency services (ambulance, mountain rescue, fire department, coast guard, police), triage nurses and physicians. As noted earlier, the type of analgesia available to a patient at different stages of care may be limited by the prescribing rights of the emergency services personnel or nurses treating them, or the availability of an analgesic on scene (particularly opioids and ketamine).

Current European guidelines

There are currently no European guidelines for the management of acute pain in an emergency situation, but a number of national guidelines are available. Evidence suggests that implementing guidelines for the management of acute pain in the emergency setting (including providing multichannel education on those guidelines to ED staff) promotes improved pain management, increased administration of analgesia and greater patient satisfaction.[36]

In 2010, the French Society for Emergency Medicine published guidelines on the safe and effective provision of analgesia and sedation in emergency medicine. Their key recommendations are the use of local and/or regional analgesia for pain management when indicated and feasible, with the use of nitrous oxide for slight trauma and

IV morphine given immediately for severe pain, alone or as part of multimodal analgesia (**Figure 1.1**).[37] After opioid titration, analgesia should be given again before recurrence of pain. They state that nurses should be able to assess and treat pain as part of a known service protocol, provided that an emergency physician can intervene without delay and at any time.[37]

An intersociety consensus conference including seven Italian interdisciplinary and interprofessional societies related to pain and emergency medicine was held in 2010 to discuss the assessment and treatment of pain in the emergency setting. In 2015, the recommendations of this consensus group were published. The Italian Intersociety recommendations on pain management in the ED setting state that the use of IV paracetamol should be considered for its opioid-sparing properties and reduction of opioid-related adverse events (AEs) (**Figure 1.2a,b**).[38] Oral paracetamol and NSAIDs are recommended for mild pain; NSAIDs, IV paracetamol and paracetamol in combination with weak oral opioids for moderate pain; and morphine and fentanyl for severe pain. They note that pain relief and the use of opioids in patients with acute abdominal pain do not increase the risk of error in the diagnostic and therapeutic pathway in adults, so such concerns should not delay analgesia.

The Netherlands Association for Emergency Nurses has published guidelines on pain management for trauma patients in the chain of emergency care. The recommendations include two algorithms for measuring pain and providing pharmacological analgesia: one for ambulance pre-hospital settings or out of hours general practitioner services and one for helicopter emergency services, (**Figure 1.3**).[39,40] According to the guidelines, pain scores must be documented (NRS is recommended) and should be assessed at a minimum of three times: at arrival, after intervention and at the end of the medical visit. Paracetamol is the treatment of choice, with additional use of NSAIDs or opioids if necessary. Fentanyl and morphine are the preferred options for severe pain during emergency care.

In Slovakia, national guidelines have been issued by the Ministry of Health that provides a scope of practice for healthcare professionals, including pre-hospital personnel.[41] For pre-hospital personnel, the Ministry recommends the administration of non-opioid analgesics and tramadol to patients intramuscularly (IM), IV or by inhalation (INH) as needed.

In the United Kingdom (UK), guidance from the Joint Royal Colleges Ambulance Liaison Committee and the Ambulance Service Association, issued in 2017, advises that all patients with pain should have a pain severity score undertaken, with a simple 10-point verbal scale usually being the most appropriate. Pain assessment should be repeated after each intervention. Balanced analgesia with a multimodal approach is recommended, utilising analgesics with different mechanisms of action. The recommendations further state that relief of pain is one of the most important clinical outcomes in paramedic practice, and that there is no reason to delay pain relief as it does not affect later diagnostic efficacy and may in fact facilitate prompt diagnosis.[42]

Also in the UK, earlier recommendations from the Royal College of Emergency Medicine best practice guideline on management of pain in adults, published in 2014, state that recognition and alleviation of pain should be treated as a priority (**Figure 1.4**).[43] This should start at triage, include monitoring of pain during the ED visit and finish with ensuring that adequate analgesia is provided at, and if appropriate beyond, discharge. For moderate and severe pain, analgesia should be provided within 20 minutes of arrival in the ED.

In the Republic of Ireland, clinical practice guidelines have been developed by the Pre-Hospital Emergency Care Council (PHECC) that cover the range of clinical scenarios encountered by pre-hospital personnel, including pain in adults and children and have been recently updated (**Figures 1.5a and 1.5b**).[44] The guidelines recommend the assessment of pain using an analogue or visual pain scale and the consideration of non-pharmacological pain management techniques such as splinting, psychological support, heat or cold therapy and patient positioning. If pain relief is inadequate, then it is recommended that mild pain is treated with oral paracetamol or ibuprofen and moderate pain is managed with inhaled methoxyflurane or nitrous oxide and/or oral paracetamol and ibuprofen. For severe pain, patients should receive intranasal (IN) fentanyl as first-line therapy and IV fentanyl or IV morphine second line; if pain persists, the addition of IV paracetamol or IV ketamine should be considered.[44] Similar guidelines, with

differences in route of administration and dosing, are recommended for children aged 15 years or younger, with the possibility to add in additional IV ondansetron if nausea occurs.

State of workforce education and quality assurance

A diverse range of barriers preclude effective emergency pain management in the ED as identified in an American study, including bias relating to race, ethnicity, gender and age; ED physicians' inadequate knowledge and formal training in the management of acute pain; prejudice against the use and prescription of opioids; and the ED environment (such as overcrowding and interruptions) and culture (such as language barriers between patients and staff, lack of health insurance and frustration with waiting times).[22]

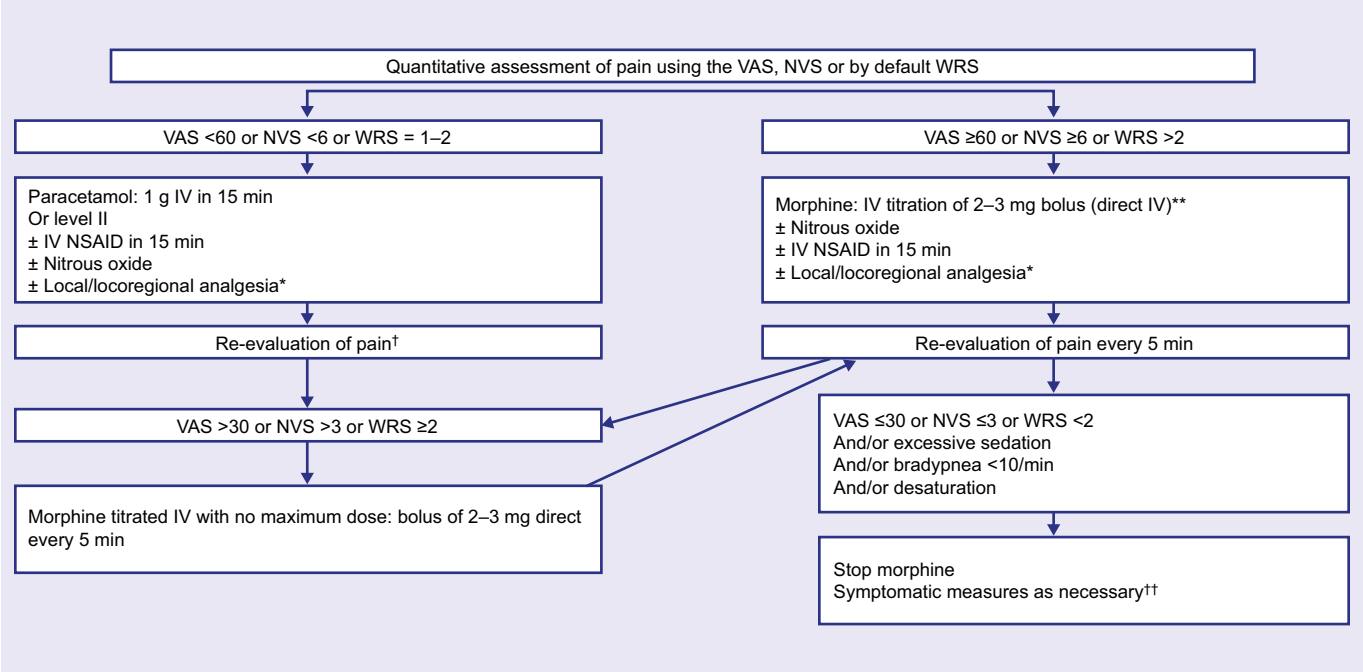
Inadequate pain management in the pre-hospital setting is associated with a number of factors, including lack of knowledge and confidence of personnel, underestimation of pain, unwillingness to administer strong doses of opioids, suspicion of potential drug-seeking behaviour in patients, and fear of side effects or injuries being masked.[13-15,18,45]

Pain management education rarely forms part of healthcare professionals' training,[22,46] and changing the practice, attitudes and behaviour of established physicians may be difficult.[22] Achieving change in practice may require the use of multifaceted strategies incorporating a range of different methods.[46] Interventions to improve pain management within the ED may need to be tailored to an individual department in order to fully address the challenges, and should be developed following an analysis of the needs and barriers to pain management that exist.[46] Currently, the knowledge of pre-hospital and ED staff about the management of acute pain is limited,[22,47,48] and many EDs don't have pain management guidelines or pain quality management programmes in place.

The current state of acute pain management in emergency situations in Europe: take-home messages

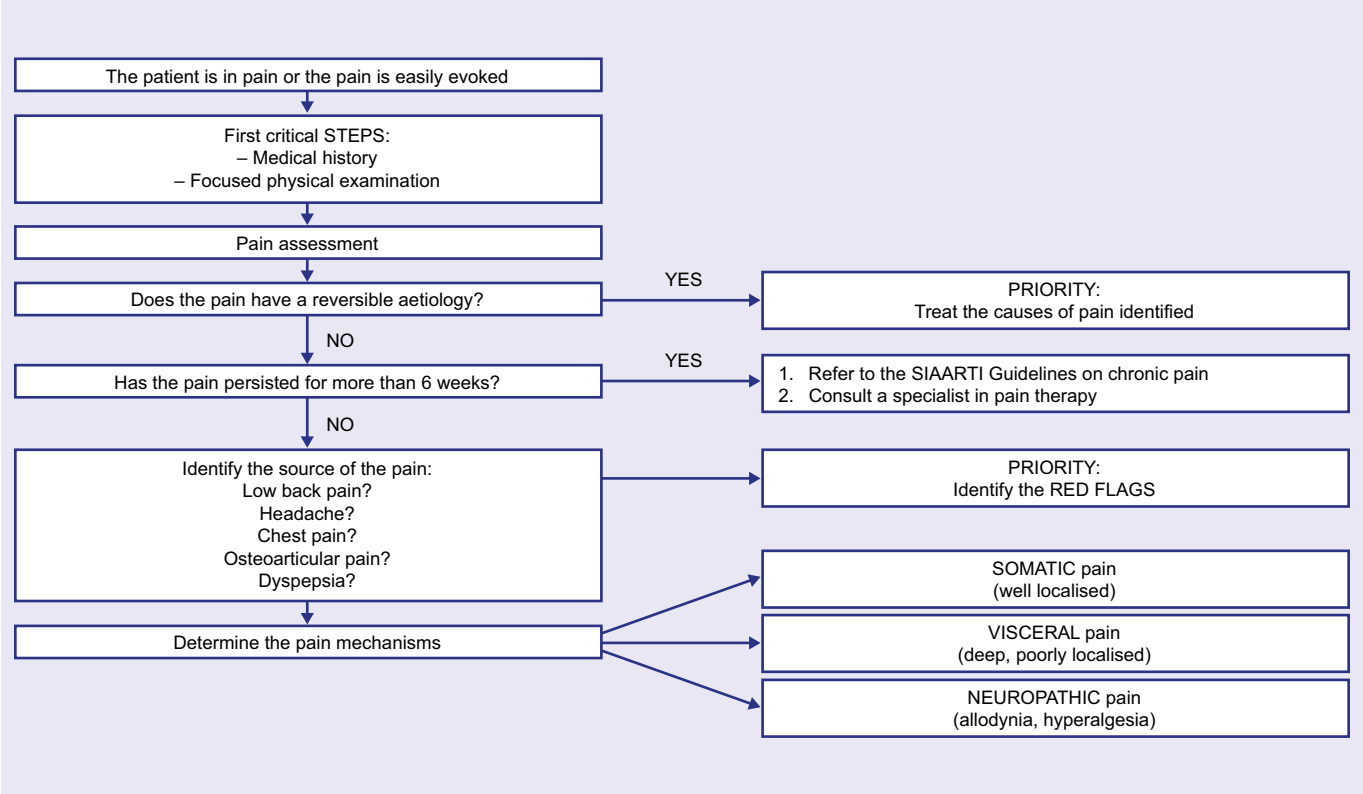
- **Acute pain is highly prevalent in emergency situations, both pre-hospital and in the ED.**
- **Acute pain is often poorly assessed and treated in both the pre-hospital and ED settings, and all too often acute pain is not assessed and therefore not treated.**
- **Barriers to adequate pain management are multifactorial and include lack of knowledge and training, reluctance to give opioids, and concerns about drug-seeking behaviour or abuse.**
- **Pain education of ED and pre-hospital staff is limited and there is a lack in systematic quality management programmes for acute pain management.**
- **There is no single current standard of care for the treatment of pain in an emergency, with management based on severity of pain, injury and local protocols.**
- **There are currently no European Guidelines for the management of acute pain in an emergency situation, but national guidelines agree that pain management should be made available to all patients and implemented with the assistance of standardised scales and tools.**
- **Changing practices, attitudes and behaviour can be difficult, and improvements and interventions should be developed with barriers to pain management and the needs of the individual ED in mind.**

Figure 1.1 French Society for Emergency Medicine guidelines for trauma pain in spontaneously breathing adults[37]



VAS, visual analogue scale; NVS, numerical value scale; WRS, word-graphic rating scale.
*Respecting contraindications of each molecule and/or technique
**Possible loading dose of morphine under constant medical supervision: initial bolus of 0.05-0.10 mg/Kg IV direct, adapted to the age and background of the patient; †Period for re-evaluation of pain dependant on the type of analgesic administered; ††Stimulation and/or ventilator support and/or IV naloxone
Reproduced with permission from *French Society for Emergency Medicine. Sédation et Analgésie en Structure d'Urgence*.[37]

Figure 1.2a Italian Intersociety recommendations on pain management in the ED setting[38]



SIAARTI, Italian Society of Anaesthesia, Analgesia, Resuscitation, Intensive Care.
Reprinted with permission of Edizioni Minerva Medica from *Savoia et al. Minerva Anestesiol* 2015;81:205-25.[38]

Figure 1.2b Analgesic recommendations

Level of pain	Analgesic treatment
NRS 1–3	**Adult patient** Oral/orodispersible paractetamol (1 g max 3 g per day) NSAIDs
	Pediatric patient (1–10 years) Paracetamol – syrup (30 mg per 1 mL) 10–15 mg/Kg (repeatable every 6 hours) – suppositories 10–15 mg/Kg (repeatable every 6 hours) Ibuprofen 4–10 mg/Kg (repeatable every 6 hours)
NRS 4–6	**Adult patient** Paracetamol IV 1 g (max 4g per day) Paracetamol in combination with weak opioids orally – paracetamol/codeine 500/30 mg (repeatable every 6 hours) – paracetamol/tramadol 325/37.5 mg (repeatable every 6 hours) NSAIDs
	Pediatric patient (1–10 years) Paracetamol IV 15 mg/Kg (repeatable every 6 hours). The maximum dose must not exceed 60 mg/Kg (not to exceed 2 g per day). Paracetamol/codeine: – syrup (25/1.5 mg per 1 mL) 1 mL per 4 Kg of body weight (repeatable every 6 hours) – suppositories 200/5 mg (repeatable every 8–12 hours) Tramadol (choose the lowest effective analgesic dose) – drops (2.5 mg per drop) 1–2 mg/Kg. The maximum daily dose must not exceed 8 mg/Kg (not to exceed 400 mg per day) – 1–2 mg/Kg IV
NRS 7–10	**Adult patient** Opioids – morphine (initial dose 4–6 mg IV) – fentanyl (initial dose 50–100 µg IV)
	Pediatric patient (1–10 years) Opioids – morphine IV 0.05–0.1 mg/Kg (perform titration to the lowest effective dose – fentanyl IV 1–2 µg/Kg

NRS, Numerical Rating Scale.
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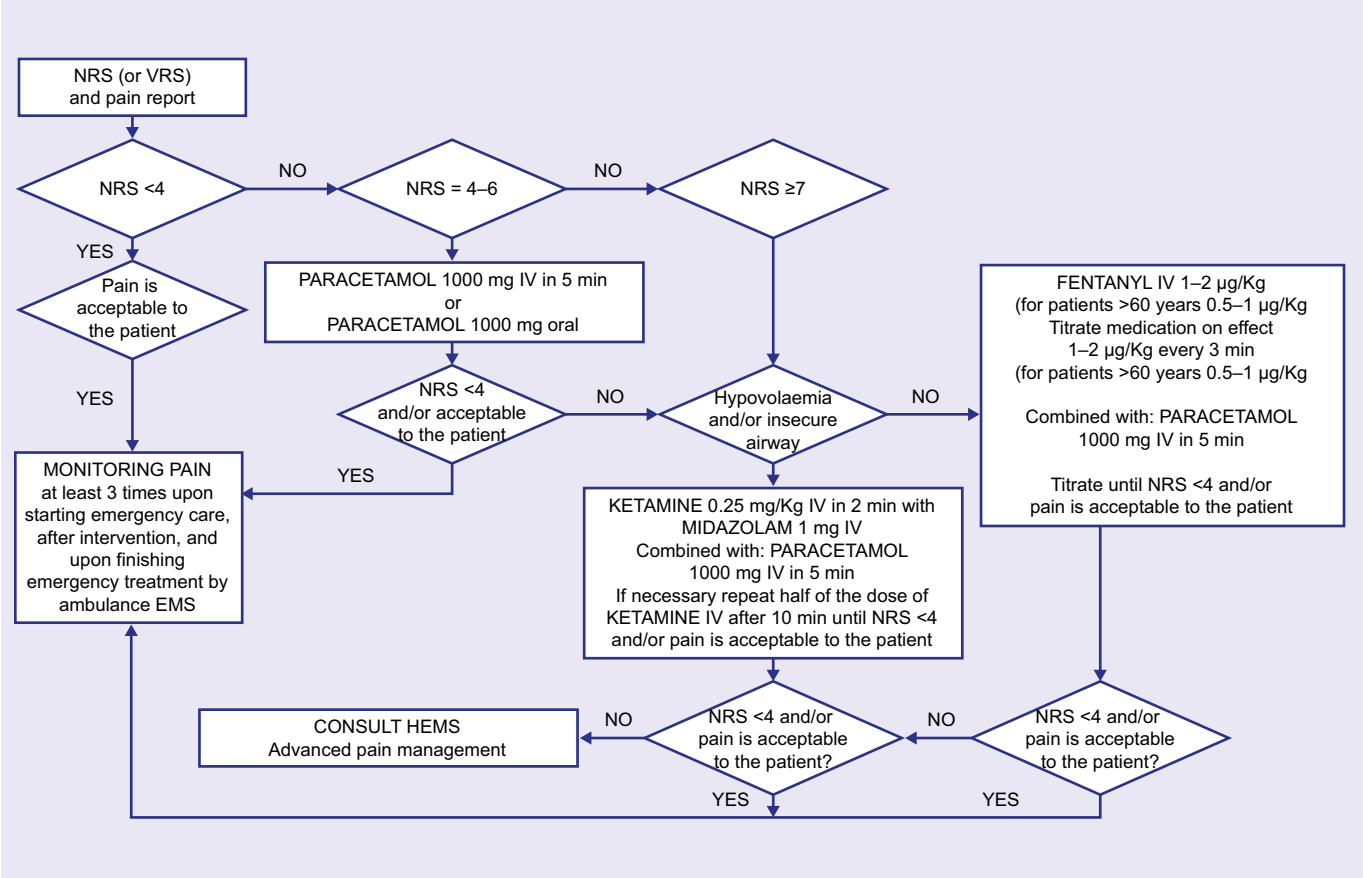
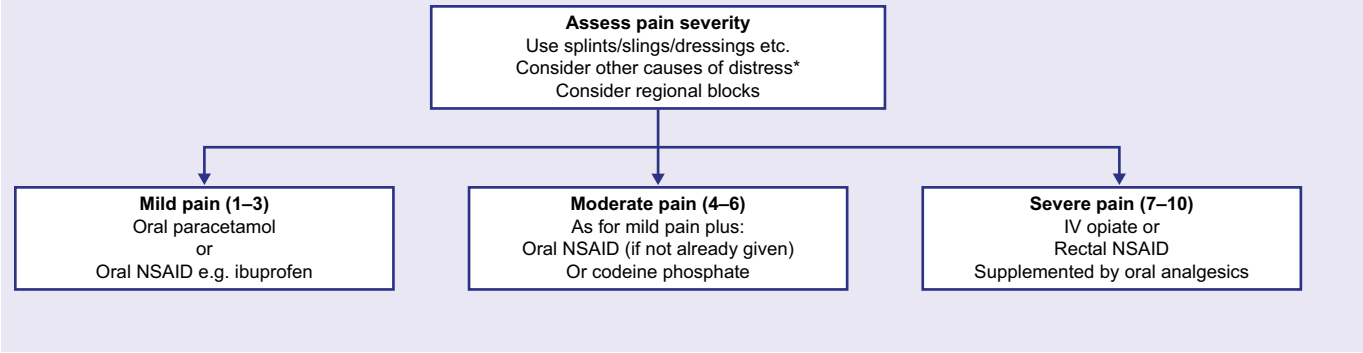
Figure 1.3 Netherlands Association for Emergency Nurses algorithm for managing pain in the chain of emergency care in pre-hospital settings[39,40]



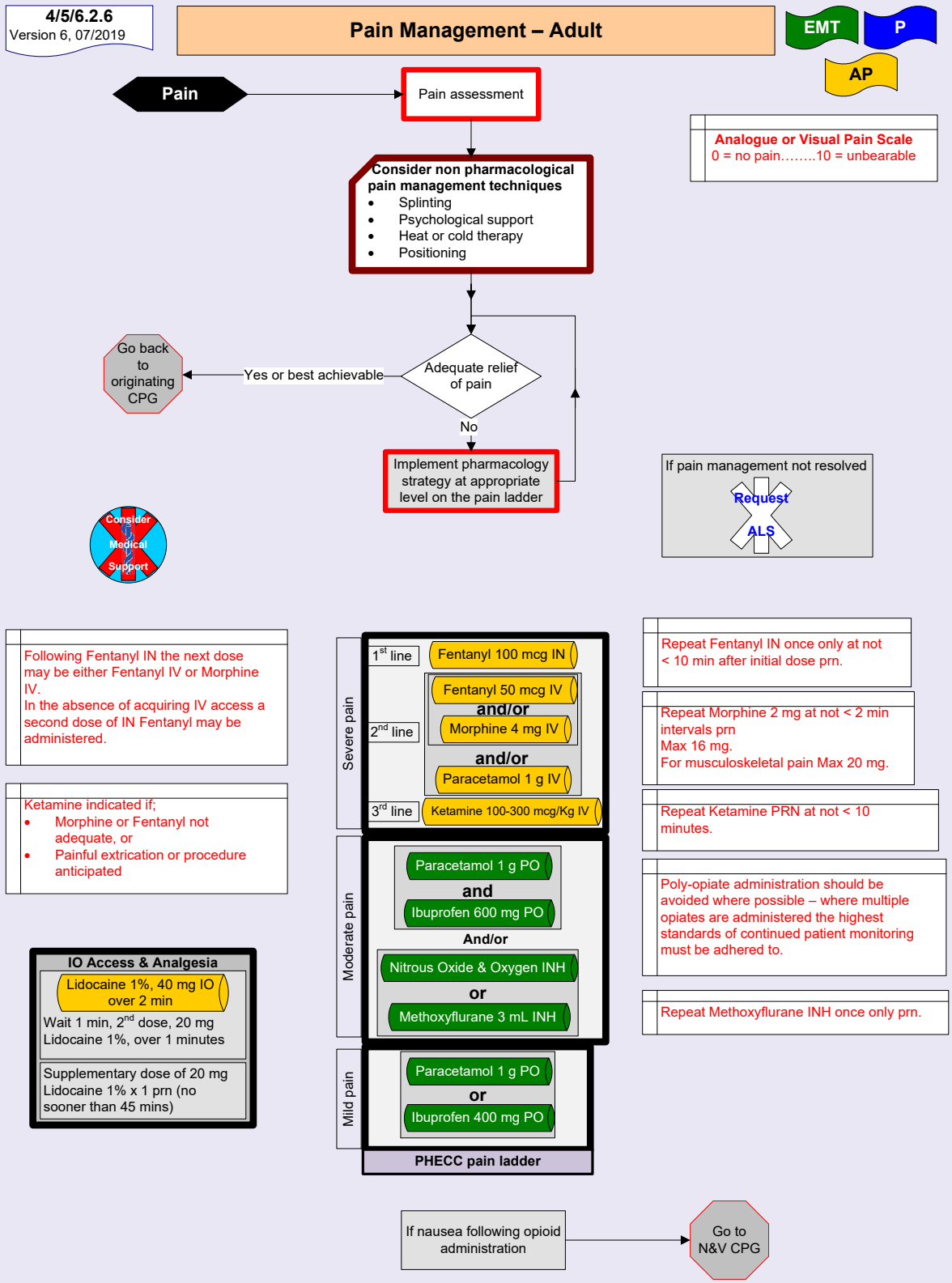
EMS, emergency medical services; HEMS, helicopter emergency medical services; NRS, Numerical Rating Scale.
Reproduced with permission from *Berben et al*.[39]

Figure 1.4 UK Royal College of Emergency Medicine best practice guideline on management of pain in adults[43]



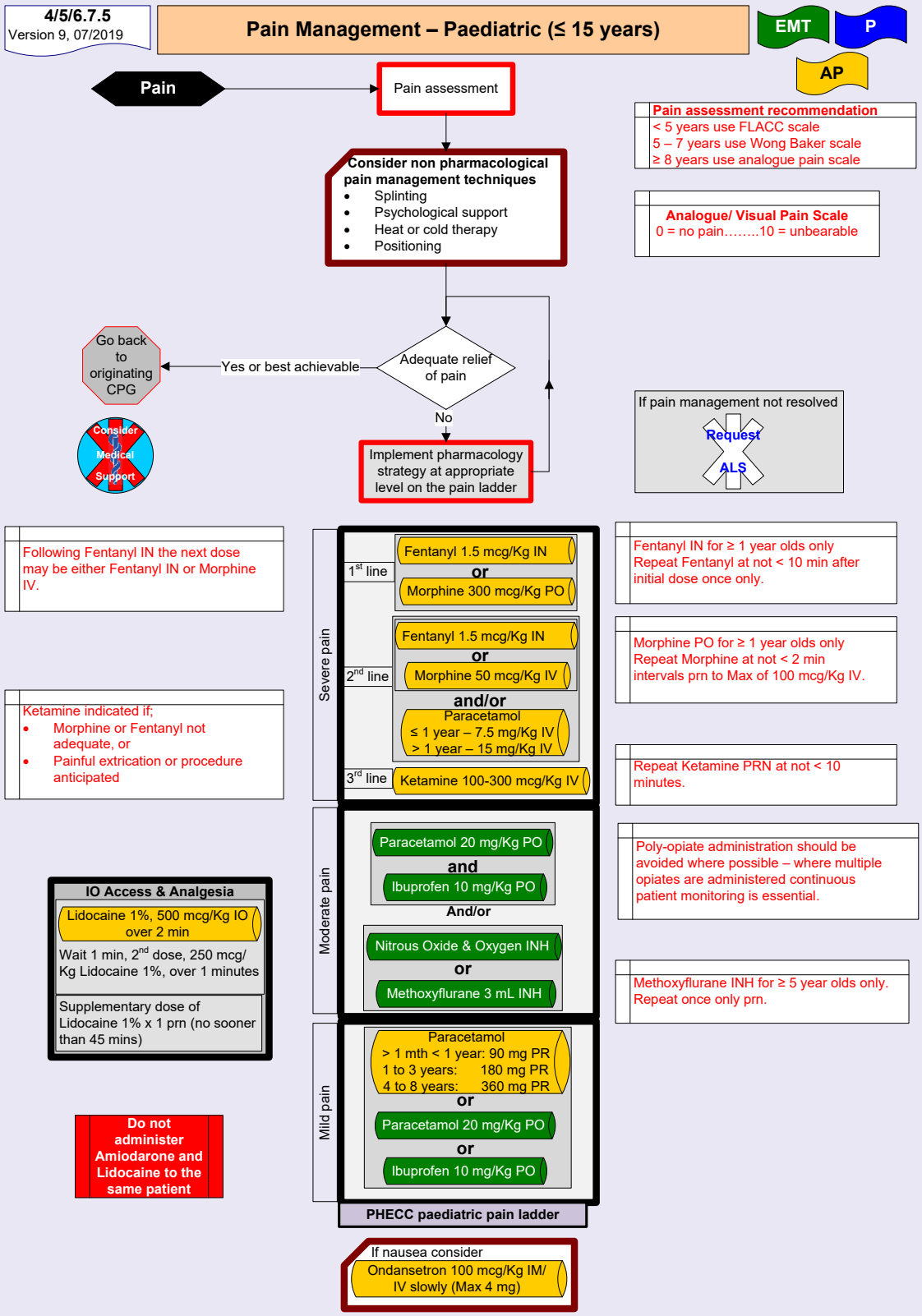
*For example, fear of the unfamiliar environment, needle phobia, fear of injury severity
IV, intravenous; NSAID, non-steroidal anti-inflammatory drug.
Reproduced with permission from *The Royal College of Emergency Medicine*.[43]

Figure 1.5a Republic of Ireland Pre-hospital Emergency Care Council clinical practice pain management guideline for adults for implementation by emergency technicians, paramedics and advanced paramedics[44]



ALS, advanced life support; AP, Advanced Paramedic; CPG, clinical practice guideline; EMT, emergency medical technician; IN, intranasally; INH, inhaled; IO, intraosseous; IV, intravenously; N&V, nausea and vomiting; P, paramedic; PHECC, (Republic of Ireland) Pre-hospital Emergency Care Council; PO, orally (per os); PRN, as needed (pro re nata).
Reproduced with permission from the *Pre-Hospital Emergency Care Council*.[44]

Figure 1.5b Republic of Ireland Pre-hospital Emergency Care Council clinical practice pain management guideline for children for implementation by emergency technicians, paramedics and advanced paramedics[44]



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ALS, advanced life support; AP, Advanced Paramedic; CPG, clinical practice guideline; EMT, emergency medical technician; FLACC, Face, Legs, Activity, Cry, Consolability (scale); IM, intramuscularly; IN, intranasally; INH, inhaled; IO, intraosseous; IV, intravenously; P, Paramedic; PHECC, (Republic of Ireland) Pre-hospital Emergency Care Council; PO, orally (per os); PR, per rectum; PRN as needed (pro re nata). Reproduced with permission from the *Pre-Hospital Emergency Care Council*.[44]

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CHAPTER 2:

Principles of acute pain management

Principles of acute pain management

The proper and effective management of pain is generally understood to be both a right for all patients, and integral to the ethical practice of medicine.[1] The underlying causes of acute pain should always be treated first (where possible). The primary aim of acute pain management is to provide treatment that reduces a patient's pain with minimal adverse effects while allowing them to maintain function. A secondary aim is to prevent the chronification of pain.[2]

Both of these aims can be more effectively achieved if pain is adequately understood and assessed. Clinician validation of a patient's pain is invaluable to assessment of pain thereby contributing to effective analgesic planning. Assessment and proper evaluation of pain is associated with more effective treatment in the pre-hospital setting.[3] Assessment methods should be relevant to the individual patient; selection of a pain measurement tool should take into account any relevant developmental, cognitive, emotional, language and cultural factors.[1] Due to the subjective nature of pain, self-reporting should be used whenever it is appropriate. However, where this is not possible – for example when patients are unable to communicate verbally – this should not be interpreted as if the individual is not experiencing pain and does not require appropriate pain-relieving treatment.[4]

Pain should be addressed as early as possible, and always within a reasonable time frame.[5] What is considered 'reasonable' will vary according to the severity of pain, but ideally no more than 20 to 25 minutes should elapse from initial evaluation to the provision of pain relief (where appropriate).[5,6] Reassessment of pain should take place at a frequency guided by the patient's pain severity, with more frequent assessments as pain severity increases.[7] Particular care should be taken when assessing and treating paediatric and geriatric patients. Both groups are often subject to oligoanalgesia, primarily due to challenges in assessing pain (especially in very young children and older patients with dementia). In addition, difficulties in obtaining intravenous (IV) access in children and concerns about potential adverse events (AEs) in the elderly are also a concern.[5] With these groups, as with pain management in any patient, the personnel involved in care must successfully liaise and communicate efficiently in order to provide safe and effective acute pain management.[1]

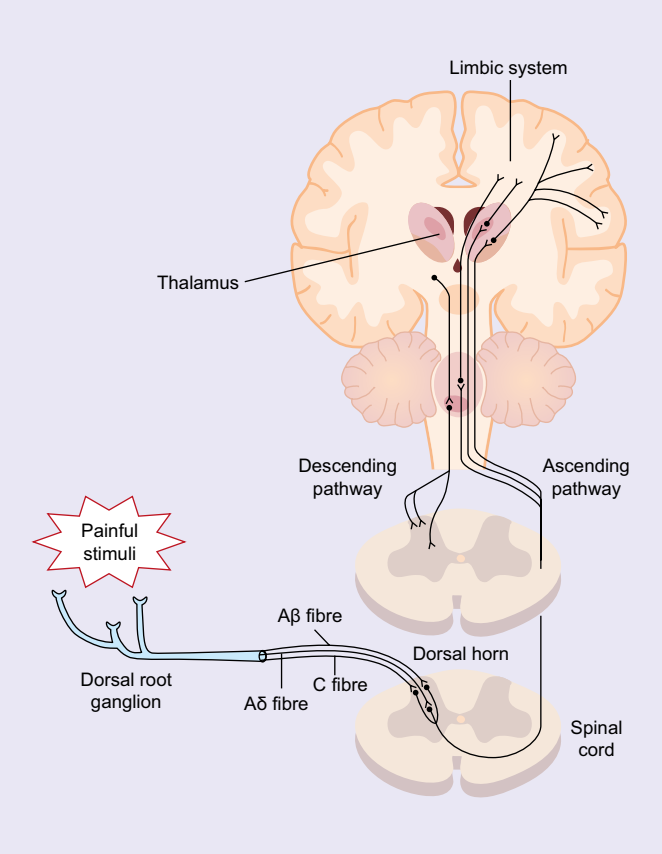
At all stages during the acute pain management process, it is imperative for clinicians to reassure patients that their pain is understood and will be taken seriously. Relief of pain facilitates patient care, since severe pain can make it more difficult to perform important tasks related to clinical management such as taking a history or performing a physical examination. Amelioration of pain also has its own medical benefits, such as reducing pain-related tachycardia in a patient with cardiac complaints.[5]

Pathophysiology of pain

While unpleasant, the sensation of acute pain serves a useful function, providing a warning of actual or potential tissue damage resulting from a specific injury or disease. It is typically of limited duration.[8] Pain is the result of the

activation of free nerve endings by tissue damage or disease.[9] Mechanical, thermal or chemical mediators such as bradykinin, substance P, histamine and prostaglandins are released from the injury site, resulting in the generation of action potentials which travel along afferent nerves to the dorsal horn of the spinal cord. There they result in the release of neurotransmitters and neuropeptides that enable the action potentials to cross into the spinothalamic tract and then ascend to the thalamus and midbrain (**Figure 2.1**).[9-11] Nociceptive signals from the thalamus are transmitted to other areas of the brain including the cortex, limbic system and frontal and parietal lobes, and it is here that the action potentials are perceived as pain.[9] The experience of pain is subjective, and can be affected by emotional factors. Stress, anxiety and apprehension – all inherently associated with trauma situations – can enhance the perception of pain.[12]

Figure 2.1 The pain pathway



Importance of effective pain management

Providing effective management of acute pain is important from the human perspective because one is providing relief from suffering. Improving patient comfort is an endpoint in itself.[5] Another, more pragmatic reason why providing appropriate analgesia is important, is that untreated or undertreated acute pain is associated with significant negative consequences, including the risk of pain chronification, delayed recovery (with an associated increased risk of infection), impaired sleep, reduced mobility and poorer quality of life.[13] Other potential outcomes of delayed or ineffective analgesia include impaired immunity, increased hospital re-admission rates, psychological impacts such as post-traumatic stress disorder, tachycardia, hypertension, increased myocardial oxygen demand, hyperglycaemia, insulin resistance, changes in fat and protein metabolism, and coagulopathies.[1,9,10,13] Control of acute pain after an initial injury can prevent the transition from normal peripheral acute pain to maladaptive sensitisation of the nervous system, which could otherwise result in chronic pain syndromes that may persist for years.[14] The chronification of pain in patients with acute pain is not rare – it occurs with varying prevalence in different categories of trauma patient, from 11% in patients with simple distal fractures of the radius, to as high as 96% in patients with spinal cord injury.[14] Avoiding the transition from acute to chronic pain is therefore an important goal. Where appropriate, a multimodal analgesic approach, using different targeted pharmacological therapies (including both opioid and non-opioid analgesics) at various time points with varying mechanisms of action and differing delivery routes, may optimise outcomes in the treatment of acute pain and help to prevent chronic pain.[15]

In addition to prevention of chronic pain, evidence has consistently shown that effective pain management can improve other short- and long-term outcomes in the ED, including sleep, physical function, quality of life and prevent the development of longer term chronic pain.[13,16,17] It is important that analgesia be provided promptly, minimal delays in analgesic administration are known to be associated with shorter ED stays.[18] In a Canadian post-hoc analysis of real-time data, patient stay in the ED was dependent on the interval length between admission and analgesic administration. Length of stay could be shortened by a median of 1.6 hours if analgesia was received within 90 minutes compared with time after ≥90 minutes, regardless of whether patients were subsequently discharged ($p<0.001$) or admitted to hospital from the ED ($p<0.05$).[18]

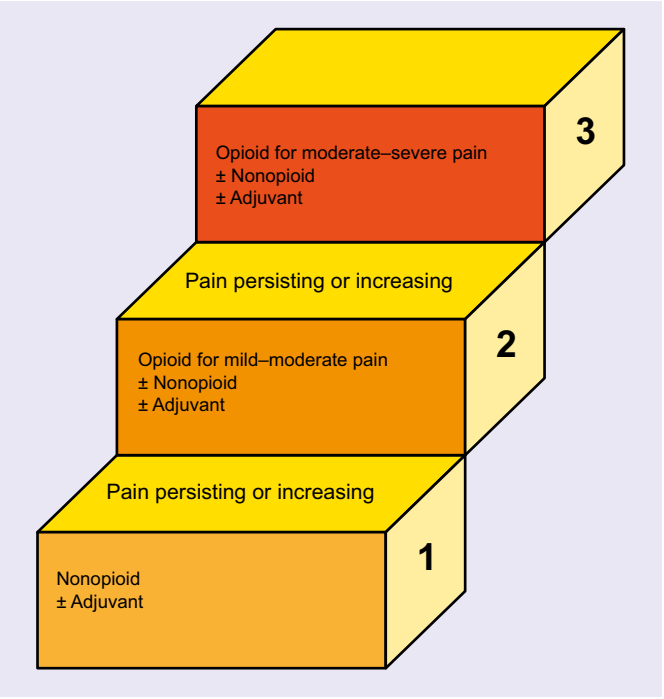
Management of pain according to the World Health Organisation (WHO) pain relief ladder

Evidence suggests that implementation of guidelines for management of acute pain in the emergency setting leads to improved pain management.[19] In a Swiss interventional study, the frequency of pain assessment, the frequency of use of analgesia and the total dose of analgesia administered all increased following the adoption of simple clinical guidelines on the treatment of pain from any cause by ED staff, resulting in higher levels of pain relief and patient satisfaction with pain management.[19]

However, in the absence of relevant or specific guidelines, the WHO pain relief ladder, which was originally designed for cancer pain, is widely accepted as a guide for the management of acute pain (**Figure 2.2**).[20,21] The WHO pain relief ladder provides a stepped approach to the management of cancer pain in which, if pain occurs, there should be prompt oral administration of drugs until the patient is free of pain.[20] Adjuvants (including antidepressants, anticonvulsants and glucocorticoids) can be used in conjunction with analgesics for pain management or to mitigate physiological processes that can perpetuate or exacerbate pain, such as oedema, swelling, anxiety and muscle contraction or spasticity.[21] To maintain freedom from pain, drugs should be given at regular intervals in accordance with their pharmacological characteristics – a 'by the clock', rather than an 'on demand as pain arises' administration. Surgical intervention on appropriate nerves may be used to provide further pain relief if drugs are not entirely effective.[20]

Since the initial publication of the WHO pain relief ladder in 1986, a number of modifications have been proposed to adapt the ladder to different types of pain, such as acute pain, and to take into account recent developments in analgesia such as nerve block techniques and sublingual and transdermal opioids.[22,23] In patients with acute pain it may be more appropriate to use the pain relief ladder in reverse, so that patients in severe acute pain begin with strong opioids, then as the pain resolves analgesia is reduced to weak opioids, and finally to non-opioids until pain is managed.[23]

Figure 2.2 The World Health Organization pain relief ladder[20]



Principles of acute pain management: take-home messages

- **Proper and effective pain management is a right of all patients experiencing pain. The key aim is to reduce pain, maintain function and minimise adverse effects.**
- **Acute pain is generally associated with injury and is of limited duration. It results from the activation of nerve endings at the site of tissue damage.**
- **Appropriate and adequate validation of the patient's pain and pain assessment is vital to effective pain management.**
- **Effective pain management can improve long-term outcomes, while untreated or undertreated acute pain is associated with significant negative impact. Long-term chronic pain may result if acute pain is not adequately controlled.**
- **The WHO pain relief ladder provides a general guide to pain management, though further modifications to the original model may be required to make it fully applicable to acute pain management.**

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CHAPTER 3:

Assessment of pain

Importance of effective pain assessment

Reliable and accurate assessment of acute pain is necessary to allow the provision of safe, effective and individualised pain management. It assists the diagnosis of the source of the pain, the selection of an appropriate analgesic and the monitoring of the response to that therapy.[1]

Pain perception is subjective and individual, which can present a challenge to healthcare professionals when it comes to understanding the degree of pain that a patient is experiencing. Self-reporting of pain should be used where possible, as proxy ratings of pain have been shown to underestimate high pain levels in some studies.[2] When selecting the pain measurement tool(s) to be used in assessing pain, the healthcare provider should take into consideration all relevant factors relating to the individual patient: developmental, cognitive, emotional, language and cultural.[1]

Reassessment of pain is as important as the initial assessment, and should take place at a frequency guided by the patient's pain severity.[3] Patients in the ED prefer pain assessment to take place approximately every 15 minutes, with more frequent assessments when pain is severe.[4] Automated pain tracker devices based on tablet computers provided to patients in the ED may be helpful to promote regular pain assessment, with a pilot project suggesting that these automated systems can improve pain care, efficiency and pain assessment documentation, and that patients find them easy to use.[5] It is important that pain assessment is done in real time, as it has been shown that patients do not accurately recall their pain levels retrospectively, even just one to two days after acute trauma.[6]

This chapter reviews the tools and scales used to assess and monitor pain in patients with acute pain in an emergency setting.

Effective patient pain history

The first element to effective pain assessment and management is an effective patient history. As a first step, clinicians should reassure patients that their pain will be taken seriously and that the impact of their pain and its requirement for treatment is understood. Respectful validation of a patient's suffering is invaluable to assessment and will lead to effective analgesic planning. It is important to ensure that careful attention is paid to the patient's reported symptoms in order to direct the process of the physical examination and lead towards a pain differential diagnosis. During the pain history, an understanding of the following is required: location of pain; temporal characteristics; aggravating and alleviating factors; impact of pain on function and quality of life; past treatment and reports; and also patient expectations and goals for their pain *(*for more information see **Chapter 6** – Pain Management, Table 6.1, see page 83).

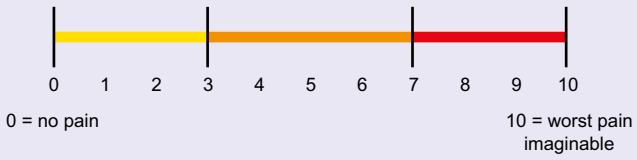
Categorical pain scales

Categorical scales use words to convey the degree of pain or pain relief. A verbal descriptor scale is the most commonly used type of categorical pain scale.[1] This type of scale typically includes four to five descriptors from 'no pain' through to 'excruciating/agonising pain' (or similar terminology), which can be converted to numeric scores for the purposes of recording a pain rating and comparison of a patient's pain over time. Pain relief (rather than pain intensity) can also be graded using a verbal descriptor scale. The benefit of categorical scales is that they are quick and simple to use; however, they are less sensitive than numerical scales due to the reduced number of possible options.[7,8] They also rely on the patient correctly interpreting and understanding the descriptor words, so may not be suitable for all patients, particularly where there is a language barrier.

Numeric rating scales

Numeric rating scales (NRS) can be delivered verbally or in a written format. In either format, patients are asked to rate the intensity of their pain according to an 11-point scale of 0 (no pain) to 10 (worst pain imaginable) (**Figure 3.1**).[8,9] Mild pain would be considered as a pain score of 1–3, moderate pain a score of 4–7 and severe pain a score of >7.[10] Patients may be asked to rate their average pain over the past 24 hours or week, but the results are most accurate when the scales are used to record the patient's impression of their current pain intensity.[6]

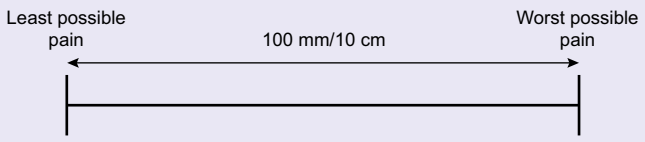
Figure 3.1 The numeric rating scale (NRS-11)



Visual analogue scale

The visual analogue scale (VAS) is the most commonly used scale for rating pain intensity in clinical trials.[1] It takes the form of a 100 mm/10 cm horizontal line, the left end of which is defined as 'no pain' and the right end as 'worst possible pain', with no other tick marks along the length of the line (**Figure 3.2**)[9]. The patient marks the point along the line that they feel corresponds to the level of pain that they are experiencing, and the pain score is recorded as the measurement in millimetres or centimetres from the left end of the scale to the patient's mark. The VAS has similar sensitivity to the NRS when comparing acute postoperative pain intensity, and a greater sensitivity than a 4-category verbal descriptor scale.[7] A VAS rating of more than 70 mm is predictive of the need for a high (e.g. >0.15 mg/Kg) morphine dose to achieve pain relief, and can be considered indicative of severe pain.[11] A reduction in pain intensity of 30%–35% on the VAS has been rated as clinically meaningful by patients with acute pain in the ED.[12] When the VAS is used in clinical practice in the ED, displaying a patient's changing pain scores as a graph over time, it may lead to increased physician awareness of pain scores and the need for earlier analgesia, as well as greater patient satisfaction with pain care.[13]

Figure 3.2 The visual analogue scale (VAS)



Assessments of functional impact of pain

The functional activity scale (FAS) is a simple 3-level categorical score used to assess whether a patient can undertake appropriate activity at their current pain level and trigger retreatment if activity is curtailed by pain.[1] The patient is asked to complete a particular activity or is assisted in doing so, and their ability to do so is assessed as A (no limitation due to pain), B (mild limitation, with the patient able to complete the activity but experiencing moderate to severe pain in the process) or C (significant limitation, where the patient is unable to complete the activity due to pain). The patient's FAS score can then be used to assess the effectiveness of pain treatment on function. However, this scale has not yet been independently validated.[1]

Assessment of pain in special situations

It is important to recognise that impaired or limited ability – or indeed, complete inability – to communicate verbally does not mean that an individual is not experiencing pain and in need of appropriate pain-relieving treatment.[14] Special consideration must therefore be given to the assessment of acute pain in babies and young children, the elderly (particularly those with dementia) and unconscious or sedated patients.[14] Other circumstances that pose a particular challenge when assessing pain include breakthrough pain in cancer patients or those with chronic non-cancer pain, and in patients with a history of, or current, drug misuse.

Paediatric patients

Evidence suggests that children who present to the ED receive suboptimal assessment and relief of pain, partly due to a failure to use appropriate pain assessment tools.[15] However, a range of paediatric pain rating scales have been developed and are available for use in children from neonates up to adolescence (at which stage adult rating scales can be used).[16]

Scales for the assessment of the intensity of acute pain in neonates include the Premature Infant Pain Profile (PIPP), the CRIES (C-Crying; R-requires increased oxygen administrations; I-increased vital signs; E-expression; S-Sleeplessness) the Neonatal Facial Coding Scale (NFCS).[16] Since such young babies are unable either to communicate verbally or to understand and follow instructions, these scales rely on observations of variables such as the presence or absence of crying, facial expression, heart rate and other vital signs.[16] Another commonly used pain scale which does not rely on the ability of the patient to communicate with the assessor is the FLACC scale. This can be used to assess pain in children between the ages of two months and seven years, in children with cognitive impairment,[17] or in individuals of any age that are unable to communicate their pain.[18] The FLACC scale has 5 criteria (facial expression, position/movement of legs, overall activity, presence/degree of crying, and ability to be consoled or comforted) which are each assigned a score of 0, 1 or 2, giving a total score in the range of 0–10, with 0 representing no pain.[18] A modified version of the FLACC scale, FLACC-R has been developed for children with cognitive impairment.[19]

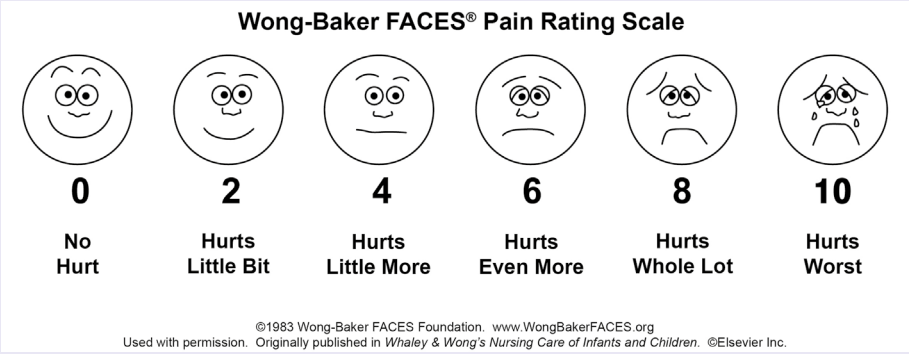
For those patients with some, albeit limited, ability to communicate, such as young children, the FACES pain scale (FPS) can be very useful (**Figure 3.3**).[20] Patients are shown a range of faces showing varying degrees of distress, and asked to select the expression that corresponds to the amount of pain that they are currently experiencing.[20]

Geriatric or cognitively impaired patients

Pain is generally underreported in the elderly, even those with normal cognition.[21] Identifying and measuring pain in cognitively impaired elderly individuals is an even greater challenge.[22] Nonetheless, it is of great importance since it is estimated that up to one-half of people with cognitive impairment also suffer from pain,[23] and untreated pain in the elderly leads to increased disability and decreased quality of life.[21,24]

Evidence is available to support the reliability and validity of many assessment tools that use patient self-reporting, even in older people with mild-to-moderate cognitive impairment,[25-27] and it is recommended that these should be used wherever possible.[23] Opinion is divided as to whether self-reporting tools can be successfully used in those with advanced cognitive impairment.[22,28] Several of the pain scales used in younger adult populations or children are

Figure 3.3 Wong-Baker FACES scale (FPS)[20]



Reproduced with permission from Wong-Baker FACES Foundation http://www.WongBakerFACES.org.[20]

appropriate in elderly patients, including verbal descriptor scales, the NRS and the FPS. Of these, verbal descriptor scales have been shown to be most sensitive and reliable in older adults, including those with mild-to-moderate cognitive impairment.[29]

A number of different specialist pain assessment tools are available for use in non-verbal older adults with dementia.[30] The PAINAD scale is an observer-rated tool for assessing pain-related behaviour, and is partly based on the FLACC scale. It consists of five items: breathing, negative vocalisation, facial expressions, body language and consolability. Each item can be rated from 0 to 2, to generate a score ranging from 0 to 10.[24] Other physiological signs that can give a useful indication of the presence of pain in elderly patients – particularly those with cognitive impairment – include hypertension, tachycardia or bradycardia, sweating and increased muscle tone.

Sedated or unconscious patients

Assessing pain in patients who are critically ill is a challenge, particularly where patients are non-verbal due to sedation or lack of consciousness.[31] This is especially true in the pre-hospital setting, where altered mental state is the main risk factor for patients receiving no pain assessment.[32] The behavioural pain scale (BPS) has been validated for use in critically ill, sedated and mechanically ventilated patients (**Table 3.1**). The BPS score is calculated as the sum of three subscales (facial expression, upper limb movements and compliance with mechanical ventilation), each with a score ranging from 1 to 4.[31] Of the pain scales developed for use in adult patients under intensive care, the BPS is considered to be one of the most valid and reliable.[31,33]

Table 3.1 The behavioural pain scale (BPS)[31]

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g. brow lowering)	2
	Fully tightened (e.g. eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Reproduced with permission from *Payen et al*.[31]

Breakthrough pain

Breakthrough pain is defined as 'a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger despite relative stable and adequately controlled background pain'. It occurs in patients with cancer at a rate of ~60%,[34] but evidence relating to its prevalence in chronic non-cancer pain is currently lacking. Breakthrough pain impacts patients' ability to function, as well as their mood and quality of life.[35] A diagnostic algorithm has recently been developed to diagnose breakthrough cancer pain,[36] but tools such as these should be used in conjunction with detailed clinical assessment and, importantly, with information from patients and their carers.[37,38]

Pain in patients with active or previous drug misuse

A challenge in the ED is patients seeking opiates who report pain. For these patients, it is essential to differentiate between the patient with genuine pain and those falsely reporting pain only to gain medication. It is recognised that patients who are seeking opiates will present with very plausible pain symptoms and discriminating the patient's report from the patient's clinical symptomology can be difficult. Features of patients seeking opiates falsely reporting pain may include: repeated visits to the ED; cutaneous signs of drug abuse (e.g. skin tracks from IV or subcutaneous [SC] injections); assertive or aggressive patients who may be emotionally labile; current intoxication; an unusual level of knowledge about controlled substances; a very 'textbook' medical history or evasiveness/vagueness in response to questioning; reluctance to provide additional information (e.g. primary care practitioner details); and requests for a specific controlled drug with no interest in or reluctance for other suggested medications. Clinical judgement, experience and careful observation – particularly when the presenting patient believes that they are not being observed by healthcare professionals – can help to distinguish between genuine patients and opiate-seeking individuals.

Other assessments in patients in the ED

Besides pain intensity, a number of other factors can affect a patient's requirement for analgesia; for example, the degree of consciousness or level of agitation. In order to determine the analgesic needs of patients with trauma pain within the ED, several scales assessing factors other than pain are often used to evaluate patients. The Glasgow Coma Scale (GCS) was developed to assess the depth and duration of impaired consciousness and coma. It evaluates consciousness and neurological function using a numerical scale for a range of behavioural parameters (eye opening, verbal response, motor response).[39] The Ramsay Scale includes six levels of sedation, three relating to a conscious patient, and three to a sleeping patient. Patients are scored according to their levels of alertness and agitation, from level 1 (patient awake, anxious, agitated or restless) to level 6 (patient asleep, with no response to stimulus).[40] The Richmond Agitation Sedation Scale (RASS) is a 10-point sedation scoring system which evaluates patients based on observation of their level of alertness and behaviour, and according to their responses to verbal cues and (if unresponsive to verbal cues) physical stimulation. Scores range from +4 (combative, violent) to −5 (unrousable, unresponsive), with a score of 0 indicating an individual demonstrating alert calm.[41]

Assessment of pain: take-home messages

- Regular, accurate assessment of pain is required to improve acute pain management.
- For adults and children able to verbalise their pain NRS and VAS pain scales are recommended.
- In patients who are non-verbal, such as young children age appropriate observational scales can be used for example Wong-Baker FACES scale, FLACC and CRIES and for those with cognitive impairment FLACC-R.
- In adult patients with mild cognitive impairment patient self-reporting should be considered. In patients with more severe impairment observational scales such as Wong-Baker FACES scale may be appropriate but consider the use of specific scales such as PAINAD which is based on the FLACC scale and is fully validated.
- In unconscious or sedated patients, the use of the observational BPS should be considered – this scale was developed and validated for use in critically ill, sedated, mechanically ventilated patients.

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The content of this chapter remains consistent to that developed in 2020

CHAPTER 4:

Non-pharmacological therapies in acute pain

Current non-pharmacological therapeutic options in acute pain

While pharmacological analgesics are essential for the management of pain in the ED, the place and importance of non-pharmacological treatments should not be overlooked.[1] Such therapies are increasingly being used alone or in combination with pharmaceutical agents as part of a multimodal approach to managing pain. This chapter reviews the main non-pharmacological therapies currently available to manage acute pain. Published clinical evidence on the use of these therapies in a pre-hospital or ED setting is limited in some cases; what evidence is currently available is presented in **Table 4.1** (*see page 29*).

Psychological interventions

Sharing information

Providing patients with procedural information (a summary of what will happen during a treatment) and sensory information (a description of the sensory experiences that a patient might feel during treatment) appears to positively affect outcomes and leads to reductions in reported pain and pain medication requirements, improvements in postoperative recovery, and reductions in length of hospital stay.[2,3] A Cochrane review of studies testing preoperative psychological interventions such as sharing information included a meta-analysis of 38 studies measuring the effect of these strategies on postoperative pain. Psychological preparation techniques were associated with lower postoperative pain, with similar results across all techniques used.[2] However, the level of evidence available was low with a high potential for bias, and it came primarily from studies in adults undergoing elective surgery, rather than the emergency setting.[2]

It should also be considered that, for some patients, receiving too much detailed information may increase anxiety, so the approach to sharing information might have to be adjusted according to the individual patient's coping strategy.[4]

Relaxation (stress and tension reduction)

The use of relaxation training can help patients to reduce stress and tension through techniques such as focussing on breathing patterns, concentrating on mental imagery of relaxing scenes and gradually releasing of muscle tension throughout the body. Music often forms an important part of the relaxation process. There is some evidence to suggest that the use of relaxation techniques can reduce anxiety and pain,[5-10] although once again the setting for these studies is generally postoperative pain relief rather than emergency analgesia. Indeed, relaxation techniques generally require practice on the part of the patient,[4] and may therefore have limited immediate use in an emergency situation. They may, however, be of value later when the patient is recovering.

Hypnosis

Hypnosis has a long history of use in acute pain conditions.[11] In the past, the design of studies on the use of hypnosis in acute pain lacked scientific rigour. However, there are some randomised clinical trials (RCTs) that report a significant

effect of hypnosis on acute procedural pain as well as chronic pain conditions.[12] A review on the use of hypnosis to relieve pain in clinical settings (including invasive medical procedures, burns wound care, labour and bone marrow aspiration) provided moderate support for the use of hypnosis in the treatment of acute pain.[12] In 12 of 19 studies reviewed, hypnosis was more effective in reducing pain scores than the comparator treatments which included no treatment, standard care or other psychological interventions.[12]

Similarly, a meta-analysis of 18 studies of hypnotically induced analgesia, that included 933 participants, revealed a moderate to large effect of hypnosis on pain, supporting the efficacy of hypnotic techniques for pain management.[13] Types of pain included burn, coronary pain and headache, as well as experimental pain stimuli such as cold and focal pressure.[13]

Evidence from studies in paediatric cancer patients undergoing lumbar puncture and venepuncture suggests that the addition of hypnosis to the use of analgesic cream results in less pre-procedural anxiety and less procedural pain and anxiety.[14,15] However, an RCT in children with acute burns undergoing dressing changes found that although hypnosis was able to decrease pre-procedural anxiety and heart rate it did not significantly reduce pain intensity or accelerate wound healing.[16]

Attention control methods

Attention-based techniques to control pain include distraction techniques, concentration on imagined scenes or sensations, focus on external stimuli such as music or odours, or techniques to change the patient's emotional state to a more peaceful and comfortable one.[4] Attention control techniques including the use of imagery, music and jaw relaxation have demonstrated benefits in acute postoperative pain in a number of older studies.[17-19] In a laboratory-based study, distraction led to lower intensity of acute pain induced by a thermode in 109 female participants.[20] In a systematic review of 42 RCTs, distraction using music reduced perioperative pain and anxiety in approximately half of the studies included.[21]

In children, distraction therapy can be very effective and is a technique often used in paediatric medicine. Distraction may include controlled breathing (blowing an imaginary balloon or feather or using physical items like blow pipes), books appropriate to the child's age, games and puzzles, either listening to or singing along with music, and toys, such as touch and feel toys or finger puppets.[21-24] A systematic review of 59 studies with 5,550 participants concluded that distraction is effective in needle-related procedure-related pain in children and adolescents aged between 2 and 19 years.[24]

For babies, breastfeeding or bottle feeding of sugar sweetened water can be effective, as can non-nutritive sucking on pacifiers or non-lactating nipples. In older children, distraction may be possible through coaching or coping statements, watching video, playing video games or virtual reality.[25] Interactive distractions such as playing video games are more beneficial than passive distractions like watching videos.[25] Virtual reality is emerging as a potentially effective technique to distract patients from pain.[26] It has been used successfully in an RCT in endoscopic urological surgery and found to be comparable to midazolam sedation in mitigating pain during surgery.[22]

Cognitive behavioural intervention

Cognitive behavioural therapy (CBT) is a psychological technique that includes cognitive and behavioural modifications of specific activities to reduce the impact of pain and disability and overcome barriers to physical and psychosocial recovery.[27] Interventions aim to reduce the distressing or threatening nature of pain and enhance a patient's sense of confidence to cope with it.[4] In chronic pain conditions such as subacute chronic neck pain and lower back pain, CBT is commonly used and there evidence of moderate strength to suggest that it has beneficial effects on pain, disability and quality of life in these conditions.[27,28] The intervention has also been successfully used in the management of postoperative and procedural pain.[4] However, there is currently little evidence on the use of CBT to address acute pain in a pre-hospital or ED setting.

Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) is a treatment that relieves pain by administering pulsed electrical currents across the intact surface of the skin to selectively stimulate non-noxious, low-threshold afferent peripheral nerve fibres in the skin. This is claimed to inhibit transmission of nociceptive information at the level of the spinal cord.[29] While a 1996 systematic review concluded that TENS did not have a significant analgesic effect on acute postoperative pain,[30] there is more recent evidence from a meta-analysis that high-intensity TENS can significantly reduce requirements for postoperative analgesia.[31] This analysis included 21 randomised, placebo-controlled trials with a total of 1,350 patients, and reported that the mean reduction in analgesic consumption following treatment was 26.5% less than placebo. In 11 of the 21 trials (n=964), high intensity stimulation was used, and in this subgroup of studies the mean reduction in analgesic consumption following treatment was 35.5% less than placebo.[31]

A Cochrane review of TENS for acute pain of less than 12 weeks' duration, including procedural pain and acute trauma such as sprains or fractures, included 19 studies and 1,346 participants.[29] The review indicated that TENS, administered as a stand-alone treatment for acute pain in adults, reduced pain intensity more than that see with placebo. Patients receiving TENS were nearly four times more likely to achieve at least a 50% reduction in pain than those given placebo.[29] However, the quality of the data was poor, and there was significant heterogeneity between trials and high risk of bias and unblinding.

A systematic review and meta-analysis of the effectiveness and safety of TENS administered to patients with acute pain in the pre-hospital setting analysed data from four RCTs in acute renal colic, acute lower back pain, traumatic hip pain and pelvic pain.[32] All studies included found that TENS led to statistically and clinically significant reductions in pain severity (pooled data: reduction in the mean VAS pain severity of 38 mm; $p<0.0001$). TENS also resulted in reduced patient anxiety.[32]

Acupuncture and related techniques

Acupuncture is a well-known traditional therapy that has been used in China for pain and other conditions for over 3,000 years.[33] More recently, acupuncture has demonstrated effectiveness versus sham for acute postoperative pain in a systematic review of RCTs, in terms of pain intensity, opioid use and some opioid-related side effects.[33] Fifteen trials comparing acupuncture with sham control in the management of acute postoperative pain were included. Significant differences on the visual analogue scale (VAS) were seen at 8 hours and 72 hours, and the weighted mean difference for cumulative opioid analgesic consumption for acupuncture versus sham was −9.14 mg at 72 hours.[33]

There are no studies on the use of acupuncture in the pre-hospital setting. This is likely to be due to obvious logistical concerns around transporting and handling patients undergoing the procedure. The related technique of acupressure (applying pressure to specific relaxation points) has, however, been demonstrated to reduce pain and anxiety during ambulance transport after minor trauma in two randomised, double-blind studies by the same group.[34,35] In the first of these trials, patients being transported to hospital for minor trauma were randomised to 'true' acupressure, acupressure using sham pressure points and no acupressure. Upon arrival at the hospital, pain and anxiety scores were significantly lower in the true acupressure group, and overall satisfaction was higher.[34] The second trial focussed on patient anxiety, and found that patients receiving acupressure during ambulance transport were less anxious, anticipated less pain from treatment at hospital and were more optimistic about their outcomes.[35]

Other approaches

Ultrasound

Ultrasound consists of high frequency sound waves directed at a specific site on the body to produce an image or to stimulate the tissue for therapeutic purposes. Ultrasound is frequently used in an emergency setting, but more often in a diagnostic or therapy-guiding capacity (e.g. ultrasound-guided nerve block) than in a therapeutic one.[36,37] While evidence exists on the use of ultrasound in the treatment of pain with acute fractures, a systematic review of 12 studies

reported no difference in pain scores between ultrasound and placebo groups at eight weeks.[38] In addition, it was noted that the quality of the studies varied considerably in terms of design, quality and risk of bias, making it difficult to draw conclusions from the analysis.[38]

Cold and heat

Cryotherapy is defined as the therapeutic application of a substance (e.g. ice pack or coolant spray) to the body that removes heat from the body, resulting in decreased tissue temperature, while heat therapy is the therapeutic application of a substance (e.g. heat wrap, bath) to the body that adds heat, resulting in increased tissue temperature.[39] The physiological effects of cryotherapy include reductions in pain, oedema, inflammation and muscle spasm, while the physiological effects of heat therapy include relief from pain and increases in blood flow and elasticity of connective tissues.[40]

There is limited evidence from RCTs to support the use of cryotherapy following acute musculoskeletal (MSK) injury.[40] In one pilot study, patients with an acute tear to the gastrocnemius muscle were randomised to receive either repeated application of crushed ice or no ice treatment. No significant differences in functional capacity, convalescence time, absence from work or pain score were seen between groups.[41] There is limited evidence to support the use of heat therapy in general; however, studies have shown heat-wrap therapy to provide short-term reductions in pain and disability in patients with acute low back pain.[40]

Traction and bracing

Skeletal traction is a common method for preoperative fracture stabilisation and pain control in patients with femoral shaft, acetabular and unstable pelvic fractures. In a prospective study of adult trauma patients, pain scores during immobilisation of isolated femur fractures were lower in patients placed in skeletal traction than patients who were splinted.[42]

Bracing may be useful to reduce pain and protect the neck, back and joints from further injury in trauma patients. However, mobilisation of joints such as the elbow should be started early following trauma to avoid long-term stiffness.[43]

Patient positioning

A systematic review of evidence for bed rest and exercise in patients recovering from acute lower back pain concluded that bed rest compared with advice to stay active has, at best, no effect, and at worst may have slightly harmful effects on acute lower back pain.[44]

In non-complex fractures it has long been established that appropriate positioning, for example with a back slab for wrist/arm fractures can alleviate pain and this is recommended widely.[45] Likewise, splints or slings may be helpful in patients with soft tissue injury in the early post-injury period in order to reduce pain and promote healing. In these instances, elevation and ice may also be of benefit.

Non-pharmacological therapies in acute pain: take-home messages

- **A number of different non-pharmacological approaches are increasingly being used alone or in combination with pharmaceutical agents as part of a multimodal approach to managing pain.**
- **The goals of non-pharmacological intervention in pain management are to decrease fear, distress and patients' anxiety.**
- **Non-pharmacological interventions often require few minimal resources and can be implemented in busy emergency settings (EDs or pre-hospital settings) and are proven effective in mitigating patients anxiety, stress and pain levels.**
- **Non-pharmacological interventions should be implemented early with patients, either alone or in combination with pharmacological options.**
- **Non-pharmacological interventions that should be considered include positioning of patients using traction or bracing, stress reduction techniques, attention control e.g. distraction, TENS and acupressure, all of which are supported by clinical evidence.**

Table 4.1 Evidence for non-pharmacological therapies for the treatment of acute pain in emergency situations

Evidence levels: IA, meta-analysis of randomised clinical trials; IB, randomised clinical trial; IIA, non-randomised clinical trial; IIB, other study; III non-experimental descriptive study; IV, expert opinion.

Therapy	Use in acute pain	Evidence	Level of evidence
Psychological interventions			
Sharing information	Postoperative pain	No evidence available in an emergency setting	N/A
Relaxation (stress and tension reduction)	Postoperative pain	No evidence available in an emergency setting	N/A
Hypnosis	Procedural pain, renal colic	In a case of pain caused by severe renal colic not relieved by pethidine, hypnosis was used to suggest that the pain felt by the patient was diminished to a mild itch. Upon exiting the hypnotic trance, the patient did not complain of any further pain while waiting to be seen by a urologist.[11]	IV
Attention control methods	Postoperative pain, procedural pain	No evidence available in an emergency setting	N/A
CBT	Postoperative pain, procedural pain	No evidence available in an emergency setting	N/A
TENS	Procedural pain, acute trauma pain, renal colic	A Cochrane review of studies of TENS for acute pain, including acute trauma such as sprains and fractures, reported a mean difference on a 100 mm VAS of −24.62 mm in favour of TENS versus placebo.[29] A systematic review and meta-analysis of studies of TENS in the pre-hospital setting included four studies and reported that TENS produced a mean VAS reduction of 38 mm ($p<0.0001$) in patients with moderate to severe acute pain, and pain scores significantly lower than placebo ($p<0.0001$).[32]	IA IA
Acupuncture and related techniques	Trauma pain	In an RCT of patients with minor trauma in the pre-hospital setting, 60 patients were randomised to acupressure, acupressure using sham points and no acupressure. On arrival at hospital, patients in the acupressure group had significantly less pain and anxiety, lower heart rate and greater overall satisfaction ($p<0.01$).[34]	IA
Ultrasound	Fracture	A systematic review of ultrasound in the treatment of fracture concluded that the benefits (including improvements in pain scores) could not be ruled out, but that the current evidence was insufficient to support its use.[38]	IA
Cold and heat	MSK injury	Patients with an acute tear to the gastrocnemius muscle were randomised to receive either repeated application of crushed ice (n=10) or no ice treatment (n=9) within six hours of injury. No significant differences in pain score were seen between groups.[41]	IB
Traction and bracing	Fracture	Patients with femoral shaft, acetabular and unstable pelvic fractures were placed into distal femoral skeletal traction (n=85) or a long-leg splint (n=35). Pain scores during immobilisation of isolated femur fractures were lower in patients placed in skeletal traction than patients who were splinted. There was no difference in pain score following mobilisation.[42]	IIB
Patient positioning	Back pain, fracture	A systematic review of nine trials including 1,435 patients with acute lower back pain or sciatica concluded that bed rest has either no effect or a slightly harmful effect on acute lower back pain compared with remaining active.[44]	IA

CBT, cognitive behavioural therapy; RCT, randomised controlled trial; TENS, transcutaneous electrical nerve stimulation; MSK, musculoskeletal; VAS, visual analogue scale.

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CHAPTER 5:

Pharmacological therapies in acute pain

Considerations for pharmacological management in acute pain in the emergency setting – the changing landscape since 2020

The landscape for acute pain management in emergency settings has changed substantially over the last 5 years. Since the previous version of these guidelines were published the opioid crisis has escalated, new treatment options have gained traction and, following the COVID-19 pandemic, the use of technology has emerged.

The impact of the opioid crisis has meant that opioid stewardship has become central to acute pain management. There is a shift away from routine opioid use due to increasing awareness of addiction risks, adverse events, and the contribution of emergency prescribing to the opioid epidemic.[1-5] Non-opioid and multimodal analgesia are now prioritised. Recent guidelines, including this one, now recommend using NSAIDs, paracetamol, and adjunctive therapies as first-line agents, reserving opioids for cases where benefits clearly outweigh risks (see **Chapter 8**).[3]

Multimodal analgesia refers to the use of two or more analgesic agents or techniques with different mechanisms of action to optimise pain relief and minimise side effects, particularly opioid-related adverse effects. In emergency settings a multidisciplinary approach integrates pharmacologic, non-pharmacologic, and procedural interventions, involving collaboration among physicians, nurses, paramedics and pharmacists.

Core components of an effective multimodal analgesia approach are:

- Pharmacological agents including paracetamol, NSAIDs, ketamine, methoxyflurane and regional anaesthesia.[6,7]
- Non-pharmacological methods including immobilisation, splinting and psychological interventions (See **Chapter 4** for more details).[3,8]
- Opioid stewardship, reserving opioids for severe pain in appropriate patients with protocols emphasising low-dose, short-duration use.[6,8]

The following are needed to support pharmacological and non-pharmacological multimodal analgesia interventions:[8,9]

- Use of standardised pain assessment tools at triage.
- Early and repeated pain reassessment.
- Nurse- and/or paramedic-initiated analgesia protocols to expedite care.
- Education and training for ED and pre-hospital EMS staff to encourage guideline adherence.

Multimodal regimens can reduce opioid consumption, shorten ED length of stay, and improve pain outcomes without increasing adverse effects.[7,10,11] Effective pre-hospital pain management requires coordination between EMS providers, ED teams, and pharmacy services to ensure continuity and appropriateness of analgesic care.[12,13]

The CERTA approach (Channels-Enzymes-Receptors Targeted Analgesia) to multimodal analgesia is recommended.[14] CERTA recommends combining analgesics with different mechanisms of action to optimise analgesia rather than relying only on dose increases (**Table 5.1**).

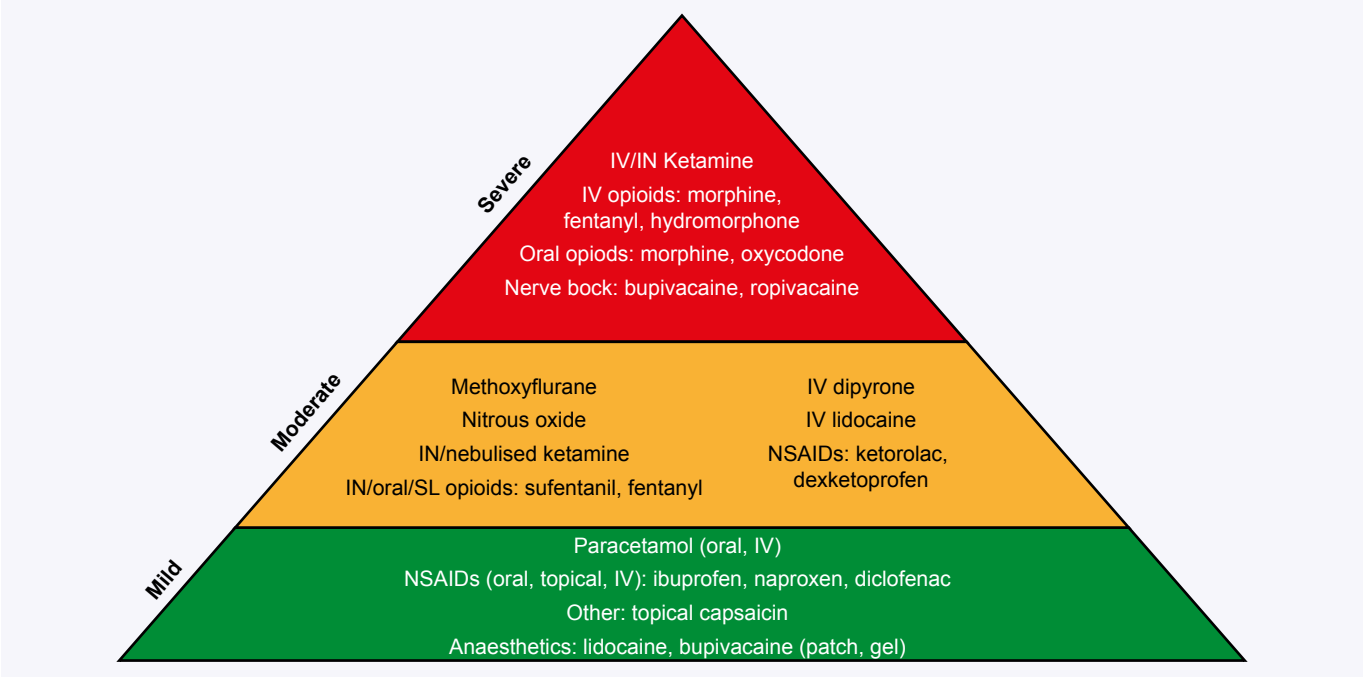
- **Channels:** analgesics that block sodium channels.
- **Enzymes:** analgesics that specifically inhibit enzyme production.
- **Receptors:** analgesics that block or activate receptors.

Table 5.1 Overview of the CERTA approach and proposed analgesics (adapted from Cisewski et al. 2019)[14]

Target	Analgesic target	Medications
Channels	Sodium channel blockers	Lidocaine, mepivacaine, bupivacaine, chloroprocaine, procaine, ropivacaine
	Calcium channel blockers	Gabapentin, pregabalin
Enzymes	COX-1, COX-2, COX-3 enzyme inhibitors	Ibuprofen, diclofenac, naproxen, ketorolac, ketoprofen, dexketoprofen Metamizole is suggested to block the COX-3 enzyme
Receptors	TRPV1 receptor agonists	Capsaicin, paracetamol
	Dopamine receptor antagonists	Metoclopramide, prochlorperazine, chlorpromazine, haloperidol, droperidol
	Glutamate/NMDA receptor antagonists	Ketamine, nitrous oxide, magnesium, propofol
	GABA receptor agonists	Methoxyflurane (probable)
	5HT1 receptor agonists	Sumatriptan
	Mu-opioid receptor agonists	Morphine, oxycodone, hydrocodone, fentanyl, hydromorphone, tramadol, buprenorphine (partial agonist), nitrous oxide (partial agonist)
	Centra alpha-2 receptor agonists	Dexmedetomidine, clonidine

The CERTA approach can be integrated into the analgesic pyramid that has been adapted from the pain ladder developed by WHO (**Figure 5.1**).[14,15]

Figure 5.1 Overview of the step-wise management of pain according to pain severity that outlines the placement of analgesics from the CERTA approach (adapted from Cisewski 2019)[14]



Alternatives to opioids such as ketamine have gained popularity in pre-hospital and ED settings in this changed environment, offering effective analgesia with lower addiction potential and fewer respiratory and cardiovascular (CV) complications.[2]

Since 2020, rapid, systematic assessment, with technological advances especially extended reality virtual reality (VR) and telemedicine with also an emergence of artificial intelligence (AI), is also playing a growing role in personalising and standardising care. However, persistent gaps remain in protocol adoption and equity, but the trend is toward safer, more effective, and more accessible pain management that is easier to prescribe safely.

Other factors influencing the management of acute pain include the ability of the treating healthcare personnel to administer various analgesics, the pain intensity of the patient as determined by pain assessment and recommendations on the class of analgesic as provided by the WHO ladder.[15] This chapter reviews the main pharmacological therapies currently used to treat acute pain in emergency situations. Updated clinical evidence on the use of these agents in the pre-hospital and ED settings is presented in the supplement to this chapter (**Chapter 5 supplement**).

Current pharmacological therapeutic options in acute pain

A wide range of analgesic agents are currently available for use in the ED and pre-hospital settings, including both opioid and non-opioid options with numerous formulations and routes of administration. However, there is great variation in the availability and use of analgesics across Europe.[16] In addition, emergency setting personnel providing pain relief across Europe vary in terms of educational level, training and job specification (e.g. nurses, paramedics, emergency physicians) which can determine their ability/authority to provide analgesics for patients in pain.[17-19]

Determining which analgesic is the most appropriate to use in patients will, to some extent, depend on the setting, whether the patient is presenting at the ED or if treatment is taking place in a potentially hostile pre-hospital environment.

Nitrous oxide

Nitrous oxide has a long history of use as an analgesic and is commonly used to relieve moderate pain in ED and pre-hospital settings.[20-22] Inhaled nitrous oxide is provided in a cylinder as a pressurised gas usually comprising a 50/50 mixture of nitrous oxide and oxygen. It is typically self-administered by the patient via a mask or mouthpiece (by adults and children most typically aged >5 years) or in young children (≤4–5 years) and can be administered by mask by healthcare professionals.

The patient controls their own intake with a demand-valve device, which discontinues the flow of gas if the patient loses consciousness.[20] Nitrous oxide has both analgesic and anxiolytic effects,[20] and is a weak anaesthetic, with a concentration of about 70% required to produce unconsciousness.[23] It has a rapid onset and offset of effect of approximately three to five minutes;[24] so does not mask signs and symptoms of illness and injury that may help provide a definitive diagnosis.[25] Side effects of nitrous oxide can include euphoria, disorientation, sedation, nausea, vomiting, dizziness and generalised tingling,[20] but the incidence of significant AEs is low.[25] Nevertheless, nitrous oxide is contraindicated in patients at risk of pneumothorax, bowel obstruction, head injuries with impaired consciousness, faciomaxillary injuries and decompression sickness, as it can diffuse into gas-filled cavities (e.g. intestine, thorax and middle ear) and increase volume and pressure.[20,23]

Nitrous oxide is known to be a potent greenhouse gas with high rates of ozone-depletion,[26] and whilst the contribution of medical nitrous oxide is very low (~0.05%) the impact is not irrelevant and should not be overlooked. In the UK, nitrous oxide was suggested to account for 75% of all emissions of anaesthetic gases, a significant proportion of which arises from pre-hospital and ED settings.[27] The recommendation from the Royal College of Emergency Medicine and a number of pre-hospital organisations in the UK is to switch from nitrous oxide to other inhalable products such as methoxyflurane, as well as non-pharmacological options and different routes of administration for other analgesics including IN, IV, intramuscular (IM) and oral.[27]

Exposure of emergency personnel to nitrous oxide has also been linked to both acute and chronic health issues. Acute symptoms include headache, dizziness, and nausea, which can impair medical staff performance and increase workplace accidents. Chronic exposure can lead to neurological complications, psychiatric issues, and an increased risk of haematological disorders such as leukopenia, agranulocytosis, and more. For instance, long-term exposure to nitrous oxide has been associated with vitamin B12 deficiency, which can result in neurological impairment. Consequently, gas scavenging and addressing nitrous oxide leakages is an imperative. Regular maintenance and leak testing of gas delivery systems, along with improved ventilation, help prevent leaks and ensure nitrous oxide is quickly diluted, particularly in confined areas like operating rooms. Staff education is equally crucial: personnel should be trained in proper equipment handling, leak detection, and response to hazards. Additionally, establishing safety protocols for cylinder handling and personal protective equipment (PPE) use can further reduce occupational exposure to nitrous oxide.

Paracetamol

Paracetamol is commonly used for treating mild-to-moderate acute pain and can be administered IV, per rectum (PR) or by oral routes.[4] It is often used in combination with opioids.[28] The maximum recommended adult dose of paracetamol is 4,000 mg/day and is considerably lower for paediatrics (toxic dose 150 mg in single dosing and maximum 80 mg/kg per day), with a risk of hepatotoxicity at higher doses.[4,29] It should be used with caution in the following individuals: alcoholics; those at risk of hepatic dysfunction or with hepatic impairment; patients with cirrhosis; and those with renal impairment.[29] Potential side effects include hypersensitivity including skin rash, erythema, flushing, pruritus and tachycardia.[30] Paracetamol is contraindicated in severe hepatic impairment or severe active liver disease.[30]

Paracetamol has been demonstrated to provide analgesia as effectively as many NSAIDs or aspirin.[29] Studies comparing oral paracetamol with NSAIDs for acute blunt minor MSK extremity trauma,[31] traumatic or inflammatory pain to the extremities (paracetamol in combination with codeine),[32] acute MSK pain[33] and pain caused by ankle sprain[34] found pain treatment with paracetamol to be at least as effective as with NSAIDs. Paracetamol IV has also demonstrated similar analgesic effects to IV morphine in patients with isolated limb trauma in a pilot study conducted in an ED in the UK.[35] In another study, IV paracetamol plus oral oxycodone was found to be as effective as IV morphine in relieving pain from acute bone fracture, although the combination was associated with more side effects (namely nausea and itching) than morphine.[36] However, a systematic review of evidence for analgesics in acute trauma pain showed clinically significant pain relief in only 2 out of 4 studies with paracetamol.[37] In addition, paracetamol does not have the anti-inflammatory properties of NSAIDs,[4,29] and has a slow speed of onset and less efficacy when taken orally.[24]

There has been debate about the potential for paracetamol to be opioid sparing, which is being disputed in published literature. One study of paracetamol plus hydromorphone indicated that the addition of paracetamol did provide pain reduction that was numerically greater than opioids alone and was less likely to require rescue analgesia, but this was not statistically significant.[38] Another study compared IV opioids plus IV paracetamol versus IV opioids plus placebo.[39] Both groups provided effective pain relief with a similar onset to effect, comparable requirements for further morphine doses and comparable rate of AEs..[39] In a large study of 600 patients randomised to 5 treatment arms, paracetamol plus codeine or oxycodone was more effective than paracetamol plus ibuprofen or hydromorphone, but no treatment differences were statistically significant.[38]

NSAIDs

NSAIDs such as ibuprofen, diclofenac, ketorolac and naproxen are commonly used in both the pre-hospital and ED settings for mild-to-moderate pain, particularly with an inflammatory component.[24] They are mostly administered via the oral or IV routes.[24,40] NSAIDs inhibit the cyclooxygenase 1 (COX-1) enzyme to produce analgesic, antipyretic and anti-inflammatory effects.[29] Older data suggested NSAIDs contribute to decreased fracture healing and infection that has been a limitation to their use.[41] However we recommend the use of NSAIDs in patient suffering from fractures

where the benefits appears to outweigh the small potential risk.[42-44] They are also associated with a number of serious adverse events (SAEs), including gastritis, bleeding and renal failure.[41,45,46] However, different routes of administration may limit side effects for example sublingual ketoprofen bypasses the stomach and has fewer adverse effects, or ibuprofen with lysine salts similarly has fewer side effects.

NSAIDs should be avoided or are contraindicated in the following patient groups:[46-48]

- Elderly
- Active peptic ulceration or stomach bleeding
- Uncontrolled hypertension
- Significant renal disease or impairment
- Inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- Previous transient ischaemic attack or stroke (apart from aspirin).

Systemic NSAIDs provide comparable analgesia to one another and to paracetamol.[49-51] Addition of paracetamol was not associated with increased analgesia neither was paracetamol pre-dosing.[49,52] Studies have suggested that lower doses of ketorolac (15–20 mg) are as effective as higher doses of ≥30 mg in adults and older adults.[53,54]

Topical NSAIDs (most commonly diclofenac administered via patches, plasters and gels) have been successfully used to provide relief in acute pain due to ankle sprain and other soft tissue injuries.[55-59,60-64] There is some evidence that the degree of analgesia provided by topical NSAIDs can be comparable to oral NSAIDs.[58] Topical administration of NSAIDs also has the advantage of limiting the risk of systemic side effects associated with other routes, although this also limits their usefulness to more superficial pain.[65] They are also not appropriate for use on broken skin,[65] and should ideally not be used in cases of chest pain until coronary causes are excluded due to their potential prothrombotic effect.

Dipyrone (metamizole)

Dipyrone (metamizole) is an analgesic with minimal anti-inflammatory effects.[66] It can be administered orally, by IV infusion or SC injection. It is used in some countries for the treatment of acute pain including postoperative pain, colic, cancer and migraine,[67] but is banned in others due to its association with life-threatening blood disorders such as agranulocytosis, which are thought to have a possible association with patient ethnicity.[68,69] Dipyrone is recommended to be administered as a single dose by infusion of 1,000 to 5,000 mg, with a maximum dose of 5,000 mg.[70] Onset of effect can be anticipated within 20 to 30 minutes and the risks of hypotension can be mitigated by short infusion over 15 minutes.[70]

Opioids

Opioids are a large class of drugs that act on opioid receptors, primarily within the central nervous system, to produce an analgesic effect. They are commonly used for treating moderate-to-severe acute pain,[20] with weak opioids such as codeine or tramadol typically used for moderate pain, and strong opioids such as morphine and fentanyl for severe pain.[15] Opioids have proven efficacy in providing pain relief in emergency settings.[37] Immediate release formulations are preferred to reduce the risk of euphoria or abuse, and extended-release formulations should be avoided because of the increased risk of overdose, particularly in opioid naïve patients. Opioids can be administered via the IV, IM, IN, oromucosal (OM)/sublingual (SL), SC, transdermal, topical or oral routes, with the choice of opioid and route of administration depending on the severity of the pain and the condition and comorbidities of the patient.[15] Opioids are associated with several side effects (particularly in opioid-naive patients), such as nausea and vomiting, sedation and respiratory depression, and itching and anaphylactoid reactions.[29,71] However, nausea and vomiting may be minimised through the use of dose fractionation. Once benefits and risks of opioids have been established, they should be initiated at the lowest possible doses and titrated to effect whilst monitoring for respiratory depression, particularly in those who are opioid naïve. Determining the route of opioid analgesic delivery should be discussed with the patient

given the pain of IV or IM administration and the risk, whilst low, of infection with IM administration. When IV routes are not possible then IN, nebulised, SL or transmucosal/buccal delivery should be considered.

Several studies support the use of SL sufentanil with positive experiences reported in post-operative care, where it was associated with good efficacy, tolerability and high patient satisfaction.[72-76] These studies indicate significant pain reductions within 15 minutes with 30 µg SL sufentanil ($p<0.001$) with continued pain reductions over the course of an hour to 36% reduction from baseline in the ED ($p<0.001$).[73] Use of rescue analgesia was low, and patient satisfaction was high, and whilst the rate of AEs was also high (79% of patients), no serious AEs were reported.[73] Pooled safety analyses of all Phase 3 post-operative and ED studies indicated AEs were experienced by >60% of patients treated with sufentanil.[74] The most common AE was nausea in 34.1% of patients treated with sufentanil, but overall the evidence suggests that SL sufentanil is well tolerated.[74]

A recent study in 2024, whilst retrospective, suggests significant pain reductions for SL sufentanil when used in pre-hospital search and rescue (reduction in mean pain NRS 8.0 to 2.6; $p<0.001$) with accompanying reductions in heart rate ($p=0.004$) and systolic blood pressure (SBP $p=0.01$) but none were considered clinically significant and did not necessitate additional monitoring or intervention.[77] A review also suggests a possible role for SL sufentanil in battlefield scenarios with potential reductions in post-traumatic psychiatric sequelae.[78,79]

The published use of IN sufentanil has increased in the last 5 years with a range of studies and systematic literature reviews (SLRs) in press.[80-82] These data indicate that analgesia with IN sufentanil is superior to placebo at 30 minutes and comparable or marginally better than IV opioids. In a study against IV opioids, pain was significantly reduced in all treatment groups but VAS was statistically significantly lower in the sufentanil group (5.0 [IQR 3.0–7.0] vs 6.6 [IQR 5.0–73]; $p=0.002$) with a faster onset and durable pain relief at 60 minutes.[82]

In several recent studies high-dose IN fentanyl was effective and well tolerated in the paediatric ED[83], IN fentanyl was found to be as effective as SC fentanyl[84] and, in a SLR, as effective as standard of care comparators (oral hydrocodone, IV ketorolac, IV morphine, midazolam) in children, adults and older adults.[85]

Generally, opioids are contraindicated or should be used with caution in patients with severe respiratory instability, acute psychiatric instability or uncontrolled suicide risk, those receiving drugs capable of eliciting life-limiting drug–drug interactions, and those seeking opioids for addiction purposes.[86] In order to decrease opioid requirements, while also improving analgesia, opioids may be used in combination with other agents, such as ketamine or NSAIDs.[15,87,88]

Ketamine

Ketamine is an N-methyl-D-aspartate antagonist widely used in emergency acute pain[24] and commonly used in combat scenarios.[89] It is given via IV, IM and IN routes.[90,91]

At full doses (1.5–2.0 mg/kg IV), ketamine is used as an anaesthetic, while at lower sub-dissociative doses (0.5 mg/kg) it provides analgesia that can be opioid sparing.[24] It is as effective as morphine but with a faster onset of action.[24,92] Ketamine has a wide therapeutic index, cardiovascular stability and no incidence of respiratory depression.[24,92] Haemodynamically, it is associated with increases in heart rate and blood pressure (BP), but it is not associated with raised intracranial pressure.[24] It is worth considering that in emergency acute pain, increases in BP may be useful to support normalised BP. Ketamine is contraindicated in patients with eclampsia or pre-eclampsia, uncontrolled hypertension, severe cardiac disease as outlined in its licence.[93] However, recent literature suggests that respiratory or intracranial issues with low-dose ketamine as used in pain management is limited.[94]

Vomiting can occur in up to 30% of patients given ketamine,[95] therefore co-administration of an anti-emetic such as ondansetron is recommended.[24] In adults, ketamine is also often co-administered with a benzodiazepine to prevent emergence effects (e.g. hallucinations, vivid dreams, floating sensations and delirium), although there is no evidence to support emergence effects at lower doses of ketamine.[24,90]

Data supporting the use of ketamine in emergency settings has increased substantially in the intervening five years since the original guidelines were introduced with ketamine administered orally, by IV, nebulisation and intranasally.[96-113] Studies have established that lower doses of IV ketamine of 0.15 mg/kg are as effective as 0.3 mg/kg with comparable reductions in pain score.[97,103] Further administration of IV ketamine by bolus (0.3 mg/kg) followed by a low dose infusion (0.15 mg/kg) may provide analgesia that is more effective than a single dose of ketamine (0.3 mg/kg) but any differences are likely to be marginal.[105] Individual studies have suggested that IV ketamine is superior to IV morphine.[100] However, systematic literature reviews and meta-analysis of IV ketamine demonstrates comparable efficacy of ketamine with comparators (most commonly opioids such as morphine) often with lower rates of AEs like vomiting but potential for higher rates of agitation.[98,99,101]

A combination of IV ketamine with other analgesics such as dexmedetomidine or antipsychotic medications such as haloperidol may provide superior pain relief to morphine alone, but larger studies are lacking.[102,106]

Nebulised or IN ketamine has the potential to provide analgesia that may be easier to administer in the cooperative patient in emergency situations. Low doses of nebulised ketamine (0.75 mg/kg) have demonstrated comparable efficacy to higher doses,[109] and doses of nebulised ketamine 0.75 mg/kg were comparable to IV ketamine (0.3 mg/kg).[111] These data are supported by case series in both adults and children that demonstrate effective analgesia with no change in baseline vital signs or AEs.[107,108] Several SLRs and meta-analyses of nebulised ketamine are published and overall show that pain scores with nebulised ketamine are comparable with IV morphine.[114] IN ketamine compared with IV morphine indicates comparable or better pain relief at 30 minutes,[112] and superior analgesia to placebo.[110,115] IN ketamine has been evaluated in two SLRs and meta-analyses both of which demonstrate that ketamine is as more effective than placebo and as effective as morphine but at 120 minutes, IV morphine may provide a more durable analgesia.[113,115]

Across all studies AEs were manageable with ketamine and included dizziness, nausea and agitation with only a low incidence of hypertension, or impact on vital signs.[98,99,104,105]

Methoxyflurane

The inhalational analgesic low dose methoxyflurane has been used extensively in emergency settings in Australia and New Zealand for over 40 years and has been approved across Europe for emergency relief of moderate-to-severe pain in conscious adult patients with trauma and associated pain.[116] Methoxyflurane is self administered, in analgesic doses, via a single-use handheld inhaler to a maximum of two 3 ml vials. It provides rapid, short-term pain relief within six to ten inhalations.[117] In anaesthetic doses, methoxyflurane is associated with hepatotoxicity and nephrotoxicity.[118] However, doses used for analgesia are considerably lower and are not associated with liver or renal issues. It is contraindicated in patients sensitive to fluorinated anaesthetic agents, patients with known or genetic susceptibility to malignant hyperthermia, patients with liver damage as a result of previous methoxyflurane or halogenated anaesthetic use, significant renal impairment, altered levels of consciousness and clinically evident CV instability or respiratory depression.[117]

A range of high quality randomised clinical trials for methoxyflurane have been published since 2020. These studies indicate that compared with standard of care analgesia, methoxyflurane can provided effective and fast-onset analgesia in adults, children and older adults.[119-125] Two SLRs further substantiate these data indicating that onset to pain relief is within 5 minutes and pain reduction was maintained over 30 minutes, however pain reduction at timepoints 60 minutes and beyond was comparable with standard of care analgesics.[126,127] A recent study of methoxyflurane in adults aged >16 years (PACKMaN study) compared methoxyflurane in those receiving morphine (maximum dose 20 mg) or ketamine (maximum dose 30 mg).[128] Pain reductions was comparable regardless of drugs received, with pain reduction comparable for ketamine and morphine.[128] There were no significant differences in the incidence of AEs.[128] The use of methoxyflurane has been well established in adults within Europe and also in children in Australia and one European study demonstrating efficacy.[159,160] The MAGPIE trial evaluating methoxyflurane in children,[161] is yet to formally be published, but results from 240 children aged 6–18 years in Ireland with moderate-to-severe pain had

faster and greater reductions in pain than those treated with placebo. These results have culminated in approval for use in children in Ireland.[162,163] Despite this robust evidence base, the lack of formal regulatory approval for paediatric use of Penthrox in wider Europe remains a significant barrier, but should be considered for those children able to cope with instruction, without facial injuries.

A key advantage of methoxyflurane is its ease of use in emergency settings outside of the ED or the ambulance including first responders in hostile environments for example high altitudes, ski slopes, and hiking trails.[129-132]

Nerve blockade

Local and regional nerve blockade, using local anaesthetic agents injected directly onto or near the nerve (either as a single injection, multiple injections, or a continuous infusion), is increasingly being employed for a wide range of painful injuries and illnesses.[133,134] Regional nerve blocks should be considered for both traumatic and non-traumatic pain.

The absence of systemic sedation with nerve block analgesia makes it easier to monitor the mental status of patients with head injuries and can ease the transport and supervision of patients with acute trauma.[135] The disadvantages of nerve blockade techniques are the complexity and the invasive nature of the procedures, and the training required to achieve and maintain proficiency. Adverse effects are rare, but include infection, nerve injury and intravascular injection.[135] Local anaesthetics are contraindicated in patients with heart block or severe sinoatrial block with no pacemaker fitted, serious adverse reactions to previous local anaesthetic administration, concurrent treatment with Class 1 antiarrhythmic agents (e.g. quinidine), and prior use of amiodarone hydrochloride.[136] In addition, local anaesthetics in nerve blocks are often co-administered with epinephrine in order to slow the rate of anaesthetic absorption, and epinephrine is contraindicated in patients with pheochromocytoma, hyperthyroidism, severe hypertension or severe peripheral vascular occlusive disease.[137]

Ultrasound-guided nerve block with bupivacaine or ropivacaine demonstrates effective analgesia in a range of emergency pain situations.[138-140] Significant reductions in pain were observed early post-administration and provides analgesia that is durable up to 48 hours with a low level of AEs reported offering potential to be opioid sparing.[139,141] The potential for opioid sparing properties of nerve blockade has been shown during surgery and in the ED. In one study of fascia iliac block given in the ED for fractures (isolated femoral neck, intertrochanteric, and subtrochanteric femur) opioid consumption was significantly reduced (17.4 vs 32.0 morphine milliequivalents).[142] In patients who received nerve block in the ED, following surgery their need for opioid remained lower than those who did not receive nerve block (13.0 vs 24.0 morphine equivalents) and had a lower hospital stay overall (4.3 days vs 5.2 days).[142] Registry data of ultrasound-guided nerve blocks also suggests a low complication rate (0.4%) accompanying effective pain relief (21%–100%).[143] Overall, nerve blocks provide potential for improved analgesia that is well tolerated and can be opioid sparing. However, administration of nerve blocks requires training of ED personnel and when training is implemented one study showed an increased nerve block use of >35%.[144] Feasibility studies of training within the ED, including of nurses, have been published and indicate that training is both feasible and effective and can be implemented cost-effectively.[145,146] Procedural guidelines to support emergency physicians to implement ultrasound-guided nerve blocks are also available.[147,148]

Lidocaine

Lidocaine is a local anaesthetic which can be given via topical, IV and intra-articular routes. Data to support the use of IV lidocaine for acute trauma pain in the ED are currently limited.[133,149,150] IV anaesthetics such as lidocaine might be a good choice over IV morphine or IV tramadol with demonstrated efficacy and a fast onset to effect,[149,150] particularly when opioids are not an option for patients. IV lidocaine may be effective for specific conditions like renal colic and post-herpetic neuralgia, in patients without heart issues and trigger point injections are useful for those presenting with myofascial pain such as low back pain.

Two studies investigating IV lidocaine to relieve pain from renal colic in the ED, either alone or as an adjuvant to opioids, reported positive outcomes with lidocaine.[151,152] A randomised, double-blind study reported no significant difference in reduction in pain score between IV lidocaine and IV morphine in ED patients with acute limb trauma.[153]

A recent systematic literature review and meta-analysis[154] of 12 randomised clinical trials in 1,351 patients with abdominal, renal /biliary colic, traumatic pain, radicular low back pain among others, indicated that pain relief with IV lidocaine from pooled data is comparable to standard analgesia (typically IV morphine, with one study each for hydromorphone and fentanyl and two studies with dexketoprofen or ketorolac) at 15, 30, 45 and 60 minutes. Analysis of individual studies, did however, suggest that IV lidocaine can provide superior analgesia. There was no statistically significant difference in the requirement for rescue medication between groups for pooled data, but analysis of individual studies indicated patients treated with IV lidocaine had a higher need for rescue than control patients. The analysis indicated that there was no statistically significant difference in the incidence of AEs between patients treated with IV lidocaine or control analgesics. These data suggest that IV lidocaine is a useful option for the emergency setting with comparable efficacy to opioids, but all studies included were noted to be of moderate quality.

Several studies have shown that intra-articular lidocaine is not significantly different compared with IV analgesia and/or sedation for reduction of acute shoulder dislocation in the ED in terms of pain relief or patient satisfaction, with shorter duration of hospitalisation and lower risk of complications.[155,156] Meanwhile, topical lidocaine, delivered as a patch, has shown effectiveness in treating rib fracture pain.[157]

Lidocaine patches are used routinely for acute localised pain but have typically been prescribed in the postoperative or chronic pain settings and should be considered when systemic use is contraindicated. A systematic literature review and meta-analysis of 10 randomised controlled trials involving 523 patients suggested that lidocaine patches can be effective in the ED for acute MSK and neuropathic pain,[158] and more effective than placebo. Included studies were highly heterogeneous and so polling of efficacy data was not possible. AEs occurred at a similar rate between all patients (RR 0.9 [95% CI 0.48–1.67]) with a moderate quality for the evidence. These data suggest a role for lidocaine patches in the ED, although the supporting evidence is of low to moderate quality.

Pharmacological therapies in acute pain: take-home messages

- **A wide range of analgesic agents are currently available for use in the ED and pre-hospital settings.**
- **Multimodal analgesia combines pharmacological (NSAIDs, paracetamol, ketamine, methoxyflurane, regional anaesthesia) and non-pharmacological (immobilisation, splinting, psychological interventions, heat/cold etc.) approaches to reduce opioid reliance and improve outcomes and should always be considered.**
- **Practical and Contextual Considerations**
  - Choice of analgesic depends on setting (ED versus pre-hospital), patient factors, and available resources.
  - There is significant variation in analgesic availability and provider training across Europe.
  - Rapid, systematic pain assessment and use of technology (VR, telemedicine and AI) are emerging trends in pain management.
  - Persistent gaps remain in protocol adoption and equity, but the trend is toward safer, more effective, and accessible pain management.

- **CERTA Approach**
  - The CERTA (Channels-Enzymes-Receptors Targeted Analgesia) approach is recommended when considering multimodal analgesia, targeting pain pathways mechanistically rather than systemically.
  - CERTA integrates balanced analgesia, using agents that block ion channels, inhibit specific enzymes, or act on receptors to provide effective pain relief with reduced side effects.
  - This approach is aligned with the adapted WHO pain ladder, offering a stepwise management strategy based on pain severity.
- **Opioid Stewardship and Multimodal Analgesia**
  - The landscape of acute pain management in emergency settings has shifted due to the opioid crisis, with a move away from routine opioid use toward non-opioid and multimodal analgesia.
  - Opioids have been a mainstay of analgesia for moderate-to-severe pain in the pre-hospital and ED settings but are associated with AEs such as nausea and respiratory depression.
  - Opioid stewardship is now central, prioritising paracetamol, NSAIDs and adjunctive therapies as first-line agents, reserving opioids for cases where benefits clearly outweigh risks.
- **Pharmacological Options**
  - **Nitrous oxide:** Nitrous oxide has a long history of use as an analgesic; self-administered, rapid onset/offset, useful for moderate pain; contraindicated in certain conditions (e.g. pneumothorax, bowel obstruction).
  - **Paracetamol:** Commonly used, and effective, for treating mild-to-moderate acute pain, with options for multiple routes of administration. However there is a risk of hepatotoxicity at high doses and should be used with caution in patients with hepatic/renal impairment.
  - **NSAIDs:** Commonly used for treating mild-to-moderate acute pain, NSAIDs should be considered first-line for inflammatory pain. NSAIDs can be administered by oral and IV routes but are contraindicated in patients with peptic ulcer disease, renal impairment, and certain cardiovascular conditions including acute coronary syndrome, thromboembolism, transient ischaemia attacks and stroke.
  - **Topical NSAIDs:** Effective for superficial pain, topical NSAIDS are associated with fewer systemic side effects and should not be used on broken skin.
  - **Dipyrone (metamizole):** An analgesic with minimal anti-inflammatory effects, which is used in some countries for treating acute pain but is restricted in other countries due to the risk of rare blood disorders.
  - **Opioids:** Previously a cornerstone of analgesia they should now be reserved for moderate-to-severe pain when non-opioids fail. Benefits of opioids include a range of multiple routes for administration (IV, IM, IN, oral, transdermal or topical) but they are associated with a sizable risk of side effects (nausea, sedation, respiratory depression and addiction).
  - **Ketamine:** Effective at sub-dissociative doses for acute pain, ketamine can be delivered by a range of routes (IN, nebulised and IV) and data has shown that it is opioid-sparing with a rapid onset and cardiovascular stability. At higher doses there may be a risk of emergence phenomena.
  - **Methoxyflurane:** Self-administered inhalational analgesic that provides rapid, short-term relief, which is well tolerated. The handheld inhaler provides ease of administration and portability but methoxyflurane is contraindicated in certain conditions (e.g. liver/renal impairment).

  - **Nerve blockade:** Increasingly used for targeted pain relief, nerves blocks can be incredible effective with a low risk of AEs, can be opioid sparing, but their use requires training and the procedure for use may be complex and invasive with a potential risk of infection and nerve injury.
  - **Lidocaine:** Local anaesthetic that may be a useful analgesia in the ED, it can be administered by IV, topical, and intra-articular routes but current data, whilst promising, are limited.
- **Key Recommendations**
  - Consider and provide multimodal analgesia that considers non-opioid options and non-pharmacological methods over opioids in the first instance.
  - Use the CERTA approach for balanced, mechanism-based pain management.
  - Reserve opioids for severe pain when benefits outweigh risks.
  - Consider local and regional nerve blockade when appropriate.
  - Monitor and reassess pain regularly, integrating both pharmacological and non-pharmacological interventions.

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CHAPTER 5: SUPPLEMENT

Overview of clinical data for pharmacological treatment options for acute pain management

Evidence supporting pharmacological analgesics for the treatment of acute pain in emergency settings is included in this supplement. All evidence has been reviewed for bias and graded accordingly. For an overview of how evidence is graded as outlined previously.

Evidence for pharmacological analgesics for the treatment of acute pain in the pre-hospital and ED settings

Therapy	Route of administration	Overview of study/data	Level of evidence
NITROUS OXIDE			
	Inhaled	**Thal et al. 1979**[2] Of 47 patients with abdominal or chest pain, MSK trauma or burns treated by a mobile unit, 44 (93.6%) achieved partial or complete pain relief with nitrous oxide.	IV
	Inhaled	**Ducassé et al. 2013**[3] In patients with moderate acute pain being transported by ambulance, 67% of 30 patients treated with nitrous oxide had NRS ≤3 at 15 minutes versus 27% of 30 patients treated with medical air (p<0.001).	IB
	Inhaled	**Herres et al. 2016**[4] Significant reductions in mean pain scores at 20 minutes, sustained to 60 minutes, were reported in 85 patients in the ED with moderate-to-severe pain who self-administered nitrous oxide.	IIB
PARACETAMOL			
	Oral	**Lyrtzis et al. 2011**[5] Patients with acute ankle sprain were randomised to receive oral paracetamol (n=45) or oral diclofenac (n=45). There was more ankle oedema in the diclofenac group at Day 3 but not at Day 0, but no difference in pain reduction between groups.	III
	Oral	**Bondarsky et al. 2013**[6] In a double-blind RCT of adult ED patients with acute MSK pain randomised to oral paracetamol (n=30), oral ibuprofen (n=30) or combination (n=30), pain scores decreased over the 1-hour study period for all groups, with no significant differences between groups in terms of pain reduction or need for rescue analgesics.	IB
	Oral	**Buccelletti et al. 2014**[7] In patients with localised traumatic or inflammatory pain of the extremities treated with oral paracetamol and codeine (n=87) or oral ketorolac (n=113), paracetamol and codeine was equivalent to ketorolac in non- and post-traumatic pain, but superior in acute, fracture and muscular pain.	IIB

Therapy	Route of administration	Overview of study/data	Level of evidence
	Oral	**Ridderikhof et al. 2018[8]** Patients with acute blunt minor MSK extremity trauma randomised to oral paracetamol (n=182), oral diclofenac (n=183) or combination therapy (n=182) showed no significant differences in NRS reduction at 90 minutes, either at rest or with movement.	IB
	IV	**Craig et al. 2012[9]** Patients with isolated limb trauma and in moderate-to-severe pain were randomised to IV paracetamol (n=27) or IV morphine (n=28). There were no significant differences between groups in terms of analgesic effect at any time point measured or rescue analgesia required, but there were significantly more adverse reactions in the morphine group.	IIB
	IV	**Zare et al. 2014[10]** In patients with acute bone fracture randomised to IV morphine (n=74) or IV paracetamol plus oral oxycodone (n=79), pain scores were lower in the morphine group at 10 minutes, but similar at later time points. Nausea and itching were seen significantly more frequently in the oxycodone/paracetamol group.	IB
	Mixed (oral, IV)	**Dijkstra et al. 2014[11]** A systematic review of pain relief in emergency care in the Netherlands included 4 studies in which paracetamol was used. Pain reduction was seen in all 4 studies, but effective pain relief of more than 20 mm on the VAS or 2 points on the NRS was reported in only 2 of the 4 studies.	IV
	IV, oral	**Charlton et al. 2020[12]** Evaluation of 80 care records, 40 patients had IV paracetamol and 40 had oral paracetamol for reports of abdominal pain, infection and trauma. IV paracetamol provided significant improvements in pain compared with oral paracetamol (NRS reduction 2.02 versus 1.76, p=0.0013). No additional analgesia was required, and AEs were not reported.	III
PARACETAMOL + OPIOIDS			
Paracetamol plus hydrocodone OR codeine OR ibuprofen	Oral	**Bijur et al. 2021[13]** RCT of 600 patients randomised to 5 different regimens with NRS measured at 1 hour. No significant differences between groups were observed. • 400 mg ibuprofen/1 g paracetamol, NRS reduction 3.0 (95% CI 2.6–3.5) • 800 mg ibuprofen/1 g paracetamol, NRS reduction 3.0 (95% CI 2.5–3.5) • 30 mg codeine/300 mg paracetamol, NRS reduction 3.4 (95% CI 2.9–3.9) • 5 mg hydrocodone/300 mg paracetamol, NRS reduction 3.1 (95% CI 2.7–3.5) • 5 mg oxycodone/300 mg paracetamol, NRS reduction 3.3 (95% CI 2.8–3.7) Rescue medication was required more often in those ibuprofen/paracetamol, or hydromorphone/paracetamol compared with codeine/paracetamol or oxycodone/paracetamol. Patients in receipt of opioids were more likely to experience nausea or vomiting.	IA
Paracetamol plus IV hydromorphone	IV	**Bijur et al. 2020[14]** Double blind RCT in 159 patients, receiving 1 mg IV hydromorphone plus placebo or IV paracetamol. At 60 minutes those receiving placebo/hydromorphone had a reduction in NRS of 6.2 units and paracetamol/hydromorphone 5.4 – a difference of only 0.8 (95% CI −0.01,1.8). At 120 minutes NRS pain differences was 0.6. Patients receiving paracetamol/hydromorphone were less likely to request rescue medication at 60–120 minutes post administration (26.9% vs 37.7%) but this was not significant. The incidence of AEs was comparable in both groups, and it was clear that the addition of paracetamol did not provide superior analgesia to hydromorphone alone.	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
Paracetamol plus opioids	IV	**Blok et al. 2021[15]** Additional IV paracetamol to opioids was used to see if additional analgesia could be opioid sparing. Opioid consumption was not different between each group and IV paracetamol was not opioid sparing. There was no difference between groups as to patient being admitted to hospital from the ED and there was no difference in ED LOS. After discharge from the ED those who received paracetamol required lower opioids, but the sample size was small.	IA
Paracetamol plus IV morphine	IV	**Minotti et al. 2022[16]** Multi-centre, double-blind, randomised, placebo-controlled study. Randomised patients (1:1), aged >18 years in the ED with pain score NRS >4 received IV morphine 0.1 mg/kg plus IV paracetamol 1 g or IV morphine 0.1 mg/kg plus IV placebo. Additional IV morphine 0.05 mg/kg was administered every 15 minutes until pain relief. The aim of the study was to understand if IV paracetamol could be opioid sparing, and primary outcomes was mean morphine dose for pain relief. Secondary outcomes were total dose of morphine given, time to pain relief and AEs. Of the 202 patients randomised 177 were allocated to IV morphine plus IV paracetamol and 90 to placebo. Abdominal pain was the most common pain location, and pain score did not differ between groups. Mean morphine dose to achieve initial pain relief was comparable between both groups (paracetamol 0.15 ± 0.07 mg/kg [12 mg ± 5.8 mg]; placebo 0.15 ± 0.07 mg/kg [13 mg ± 6.2 mg]). Total dose of morphine was also comparable between groups (0.19 ± 0.09 mg/kg [15.1 mg] vs 0.19 ± 0.10 mg/kg [15.5 mg]). Similarly, time to pain relief was comparable across both groups at 30 minutes. The rate of AEs was comparable between groups (paracetamol 22.9% vs placebo 32.4%) and not significantly different. Both treatments provide excellent pain relief but are comparable with no evidence of opioid sparing in the ED setting compared with the post-operative setting, which may reflect the use of fixed opioids doses in the ED compared with post-operative dosing. The study is limited by patient heterogeneity due to pain location and potentially high doses of morphine.	IA
NSAIDS			
Diclofenac OR ketorolac	Oral	**Ortiz et al. 2010[17]** Patients with acute pain due to ankle fracture (n=60) were randomised to oral ketorolac, diclofenac, or etoricoxib. Reductions in levels of pain were similar between groups (74.5%, 74.3% and 70.9%, respectively).	IIA
Ketorolac	Oral	**Ghirardo et al. 2023[18]** Multicentre randomised, double-blind comparative study in children with acute pain in the ED aged 8–18 with limb trauma and moderate (NRS 4–6) or severe (NRS 7–10) pain. Patients received ibuprofen 10 mg/kg or ketorolac 0.5 mg/kg or placebo. Primary endpoint was reduction in pain at 60 minutes in patients in severe pain. NRS reduction for ibuprofen at 60 minutes was 2.0 (IQR 1.0–4.0) and 1.0 (IQR 1.0–3.0) for ketorolac (p=NS). At 90 minutes ibuprofen was significantly superior to ketorolac (p=0.008) with more patients having an NRS <4 (p=0.01) or <3 (p=0.01). In those with moderate pain, reduction in NRS at 6 minutes was broadly comparable and not significantly different.	IB

Therapy	Route of administration	Overview of study/data	Level of evidence
Ibuprofen or ketorolac	Oral	**Friedman et al. 2024[19]** All patients (n=307) received paracetamol as run-in therapy and those with inadequate pain relief were randomised to ketorolac or ibuprofen. A second group (n=100) received ibuprofen (n=50) or ketorolac (n=50) with no paracetamol run-in. The primary endpoint was an improvement of ≥1.3 on 0-10 pain scale. Among run-in participants who received an NSAID, 82/99 (83%) achieved the primary outcome versus 84/100 (84%) no run-in participants (p = 0.82). Among all ibuprofen participants, 44/49 (90%) randomised to run-in and 42/50 (84%) randomised to no run-in achieved the primary outcome. Among all ketorolac participants, 38/50 (76%) randomised to run-in and 42/50 (84%) randomised to no run-in achieved the primary outcome. These data indicate that using paracetamol first before NSAIDs does not improve pain outcomes.	IC
Ketorolac	SL	**Neri et al. 2013[20]** In children (4–17 years of age) with fractures or dislocations, SL ketorolac (n=64) was compared with SL tramadol (n=67). Baseline pain score was IQR 8 in both groups. At 100 minutes both groups had significant reductions in pain compared with baseline that were comparable to each other: ketorolac IQR=4, tramadol IQR=5 (p<0.001). Use of rescue medication was significantly higher in tramadol treated patients (12.3%) vs ketorolac treated patients (3.3%) (p=0.098). Rates of adverse events were not significantly different between groups, but adverse events were numerically higher in the tramadol group (4.6%) vs 0% in the ketorolac group and included two children with vomiting and one with vomiting and dry mouth.	IB
Ketorolac	SL	**Plapler et al. 2016[21]** In acute low back pain SL ketorolac over 10 days has proven to be non-inferior to naproxen, but had a faster onset to analgesia at 60 minutes for 24.2% ketorolac treated patients vs 6.5% naproxen treated patients (p=0.049).	IB
Ketorolac	SL	**Cozzi et al. 2019[22]** SL preparations of ketorolac 0.5 mg/kg (n=70), tramadol 2 mg/kg (n=70) and paracetamol 20 mg/kg (n=70) in children with abdominal pain in the ED indicated comparable reductions in pain from baseline at 2 hours. Median IQR pain scores at 2 hours were 2 for ketorolac and 3 for tramadol and paracetamol which was not significantly different. However, children treated with tramadol experienced significantly more adverse events (n=8) compared with paracetamol (n=1) or ketorolac (n=0).	III
Mixed	Oral, topical, IV	**Dijkstra et al. 2014[11]** A systematic review including 5 studies of NSAID use in emergency care reported no clinically meaningful reductions of pain >20 mm on the VAS or 2 points on the NRS.	IV
Mixed	IM, IV	**Pathan et al. 2018[23]** A systematic review and meta-analysis of 36 RCTs including 4,887 patients with acute renal colic reported a marginal benefit of NSAIDs overall over opioids in terms of pain reduction at 30 minutes; fewer rescue treatments were required, and rates of vomiting were lower with NSAIDs than with opioids. Compared with paracetamol, NSAIDs showed no difference in pain reduction at 30 minutes but a reduced requirement for rescue treatments.	IC
Ketorolac	IM	**McReynolds et al. 2005[24]** Patients (n=58) with acute neck pain of <3 weeks duration were randomised to osteopathic manipulation or 30 mg IM ketorolac and pain evaluated one-hour post-dosing on a 5-point Likert scale. Both groups had reductions in pain intensity, but pain relief was significantly superior with manipulation rather than ketorolac (pain reduction 2.8 ± 1.7 vs 1.7 ± 1.6, p=0.02).	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
Ketorolac	IV	**Hosseininejad et al. 2017[25]** Patients with renal colic (n=300) were randomised to IV morphine and ketorolac (0.1 mg/kg and 30 mg, n=100) or IV ketorolac alone (30 mg, n=100) or IV morphine alone (0.1 mg/kg, n=100) in an RCT. Pain intensity significantly superior with combination therapy compared with IV morphine alone (3.01 ± 0.98 vs 3.66 ± 1.02, p=0.012) and compared with IV ketorolac alone (3.01 ± 0.98 vs 3.68 ± 0.88, p=0.018). Patients receiving combination therapy also required significantly less rescue analgesia than those receiving morphine alone (16% vs 20%, p=0.041) or ketorolac alone (16% vs 24%, p=0.012).	IIA
Ketorolac	IV	**Sotoodehnia et al. 2019[26]** Patients with acute renal colic (n=126) were randomised to IV ketamine 0.6 mg/kg (n=62) or IV ketorolac 30 mg (n=64). Both treatments reduced pain, with the onset of pain relief with ketamine faster than ketorolac (at 5 minutes pain reduction with ketamine superior to ketorolac p<0.001). At all other time points pain reduction was comparable.	IIA
Ketorolac	IV	**Adams et al. 2019[27]** Children with supracondylar humerus fracture received ketorolac as peri-operative analgesia (n=114) vs those who did not (n=228). Mean pain rating 0–29 minutes was significantly lower in patients receiving ketorolac (VAS=0.7) compared with the control group (VAS=1.4) (p=0.017) and remained significantly lower at 30 minutes up to 120 minutes (p=0.036). Patients who received ketorolac required significantly lower doses of oxycodone (1.0 vs 1.2 doses, p=0.003), and postoperative stay in hospital was 50% shorter (13.6 hours vs 20.4 hours, p<0.001). As a result, hospitalisation costs were 40% lower for ketorolac treated patients.	IIA
Ibuprofen	IV	**Friedman et al. 2020[28]** Randomised study of ibuprofen alone compared with ibuprofen in combination with paracetamol in 2 EDs in patients with low back pain (LBP). Pain was measured 1 week after the ED visit. Ibuprofen treated patients had a mean improvement in Roland Morris Disability Questionnaire of 11.9 ± 9.7 and 11.1 ± 10.7 for those on combination treatment, there was no difference between groups (between group difference 0.8, 95% CI −3.0–4.7). At 1 week, moderate-to-severe pain was reported by 28% of those in the ibuprofen group and 28% in the ibuprofen plus paracetamol group. Among ED patients with acute, nontraumatic, non-radicular LBP, adding acetaminophen to ibuprofen does not improve outcomes within 1 week.	IC
Dexketoprofen, ibuprofen	IV	**Dogan et al. 2022[29]** Comparison in LBP of paracetamol (n=71), dexketoprofen (n=70) and ibuprofen (n=69) in the ED and pain was measured using 0–100 mm VAS. At 60 minutes all groups had significantly reduced pain (p<0.05), but there were no significant differences between groups. VAS decrease: • Paracetamol 40 mm • Dexketoprofen 42 mm • Ibuprofen 43 mm	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
Ketorolac	IV vs IM	**Platt et al. 2023[30]** Retrospective chart review in patients aged 65 years or more, presenting to the ED (pain modality was noted). Primary outcome was pain reduction measured by need for rescue medication at 30 minutes after ketorolac administration. Patient groups were: • IV ketorolac 15 mg (n=260) • IV ketorolac 30 mg (n=52) • IM ketorolac 30 mg (n=260) • IM ketorolac 60 mg (n=52) Rescue medication requirement was comparable across groups receiving high dose medication (IV 30 mg or IM 60 mg) 13.5% and low dose medication (IV 15 mg or IM 30 mg) 6.5% (p=0.094). Analgesia in any group was not affected by the presence of concomitant analgesia. The average change in pain scores was also not significantly different across high dose of low dose medication (p=0.154). • IV 15 mg or IM 30mg – pain score reduction NRS 2.9 (±3.1) • IV 30 mg or IM 60 mg – pain score reduction NRS 2.8 (±2.9) Time to pain reduction was also comparable across groups. The occurrence of AEs was low in both groups; oedema was the most commonly reported AE. Pain reduction was not dependant on the dosing of ketorolac	III
Ketorolac	IV	**Forestell et al. 2023[31]** Systematic review of 5 RCTS (n=627 patients) comparing high dose IV ketorolac (≥30 mg) and low dose IV ketorolac (10 mg or 15–20 mg). Pain scores were comparable in patients treated with low dose ketorolac (15–20 mg) and high dose ketorolac (mean treatment difference on VAS 0–100 mm was 0.05 [95% CI 4.91, 5.01]). Even at doses of 10 mg ketorolac no difference in pain score compared with high doses was noted (mean treatment difference on VAS 0–100 mm was 1.58 mm [95% CI -8.86 to 5.71]). Patients treated with low doses of ketorolac may have an increased need for rescue medication than those treated with high doses (RR 1.27 95% CI 0.86, 1.87) in some studies. Low doses of ketorolac had no impact on observed AEs such as nausea, flushing and dizziness, and no episodes of GI bleeding or renal dysfunction were reported.	IB
Diclofenac	Topical – patch	**Kuehl et al. 2010[32]** A systematic review of 8 studies of the diclofenac patch reported reductions in VAS pain scores ranging from 26% to 88% on Day 7 and 56% to 61% on Day 14. Median time to pain resolution was 3 days less than with placebo.	IV
Diclofenac	Topical – patch	**Mueller et al. 2010[33]** Post-hoc analysis of an RCT comparing the diclofenac patch (n=60) with placebo (n=60) in pain due to acute traumatic stress injury revealed that diclofenac patch was consistently superior to placebo in providing relief from pain on movement, with mean differences in VAS score versus placebo greatest on Day 2 and Day 3 of the 7-day study (both p<0.0001).	III

Therapy	Route of administration	Overview of study/data	Level of evidence
Diclofenac	Topical – patch	**Lionberger et al. 2011**[34] Multicentre, randomised, placebo-controlled study in 134 adults with acute ankle pain due to sprain. Patients with acute ankle pain caused by a minor sprain were randomised to the diclofenac patch (n=68) or placebo (n=66) daily for 7 days and pain intensity was evaluated on treatment days 1, 2, 3 and 7. Patients treated with the diclofenac patch experienced a significantly greater reduction in pain (VAS 66.9 to 10.5 on Day 7) compared with placebo (VAS 70 to 18.4 on Day 7 p=0.0008), beginning 4 hours into treatment (p=0.02). Diclofenac patch was well tolerated.	IB
Diclofenac	Topical – patch	**Costantino et al. 2011**[35] Patients with acute ankle sprain in the ED were randomised to a diclofenac/heparin (n=142), diclofenac (n=146) or placebo (n=142) plaster. The diclofenac/heparin plaster was associated with a significantly greater mean reduction in pain on movement after 3 days than the diclofenac only plaster, and both active treatments provided significantly greater pain relief than placebo.	IB
Diclofenac	Topical – patch	**Kuehl et al. 2011**[36] In patients with acute pain due to clinically significant minor soft tissue injury randomised to diclofenac (n=207) or placebo (n=211) patch, patients treated with the diclofenac patch had an 18% greater reduction in mean pain score versus placebo, and median time to pain resolution was 2 days shorter in the diclofenac patch group.	III
Diclofenac	Topical – patch	**Lionberger et al. 2011**[34] Patients with acute ankle pain caused by a minor sprain were randomised to the diclofenac patch (n=68) or placebo (n=66) daily for 7 days. Patients treated with the diclofenac patch experienced a significantly greater reduction in pain compared with placebo, beginning 4 hours into treatment (p=0.02).	IB
Diclofenac	Topical – patch	**Li et al. 2013**[37] Patients with minor soft tissue injury occurring within 72 hours of study entry were randomised to diclofenac (n=192) or placebo (n=192) patch. Reduction in pain on movement after 7 days was significantly greater in the diclofenac plaster group than with placebo, with the difference in efficacy evident after 1 day.	IB
Diclofenac	Topical – spray	**Predel et al. 2013**[38] An RCT comparing diclofenac spray gel (n=118) with placebo (n=114) in the treatment of acute uncomplicated ankle sprain found a significantly greater proportion of patients achieved at least a 50% decrease in ankle swelling in the diclofenac arm. Spontaneous pain VAS scores were significantly lower in the diclofenac group than the placebo group at all time points.	IB
Diclofenac	Topical – gel	**Predel et al. 2012**[39] Patients with acute ankle sprain were treated with diclofenac gel (2.32% diclofenac) twice (n=80) or three times per day (n=80), or with placebo (n=82). At Day 5, the reduction in pain on movement on the VAS in both diclofenac groups was almost double that with placebo (p<0.0001). By study end (Day 8), ankle swelling in patients treated with diclofenac gel (0.3 cm) was one-third that in those treated with placebo (0.9 cm) (p<0.0001). Patients treated with diclofenac gel had significantly greater functional movement that was not seen with placebo (p<0.0001). At Day 5, treatment satisfaction was “good” to “excellent” in almost 90% of patients treated with diclofenac gel but only “good” or “very good” in 23% of placebo patients (p<0.0001).	IIA
Ketoprofen	Topical – gel	**Serinken et al. 2016**[40] An RCT comparing ketoprofen gel (n=50) with placebo (n=50) in the treatment of pain due to ankle sprain reported greater reduction in VAS score in the ketoprofen arm at 15 and 30 minutes.	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
Mixed	Topical – mixed	**Lionberger et al. 2010**[41] A review of published data on the use of topical NSAIDs in the treatment of acute soft tissue injuries reported that topical NSAIDs are significantly more effective than placebo in relieving acute pain. Topical NSAIDs provided comparable pain relief to oral NSAIDs, but with fewer AEs.	IV
Mixed	Topical – mixed	**Massey et al. 2010**[42] A Cochrane review of the use of topical NSAIDs in acute pain in 47 studies and 3,455 participants reported a number needed to treat to achieve 50% pain relief versus placebo was 4.5 for 6 to 14 days.	IA
DIPYRONE (metamizole)			
	IV	**Sanchez-Carpena et al. 2007**[43] A randomised, double-blind study compared IV dipyrone (n=103) with IV dexketoprofen 25 mg (n=101) or 50 mg (n=104) in patients with moderate-to-severe pain due to renal colic. Reductions in VAS score were comparable between dipyrone and dexketoprofen 50 mg groups, though the onset of analgesia was slower, with greater reductions in pain in the first 30 minutes in the dexketoprofen groups.	III
	IV	**Peiro et al. 2008**[44] In patients with acute pancreatitis pain randomised to receive morphine (n=8) or IV dipyrone (n=8), 75% of dipyrone-treated patients achieved pain relief within 24 hours compared with 37.5% of morphine-treated patients, with a faster onset of pain relief (10 hours versus 17 hours).	III
OPIOIDS			
Oxycodone	Oral	**Fathi et al. 2015**[45] Patients in the ED with soft tissue injuries were randomised to a single dose of either oral oxycodone (n=75) or oral naproxen (n=75). Pain scores were similar between groups at all time points assessed, although more patients given oxycodone than naproxen required additional analgesia in the first 24 hours after discharge (16.0% versus 6.6%).	IB
Fentanyl	Buccal	**Shear et al. 2010**[46] Patients receiving buccal fentanyl for orthopaedic extremity pain in the ED (n=30) had a faster onset of pain relief than those who received oxycodone/paracetamol (n=30) (median 10 versus 35 minutes). Patients in the fentanyl arm also achieved a greater magnitude of pain relief and lower rescue medication rate.	IIB
Oxycodone	Buccal	**Arthur et al. 2015**[47] In an RCT in ED patients with simple MSK injury with no complicating factors, there were no significant differences in terms of respect to time-to analgesia, analgesic efficacy, side effects, and patient satisfaction between buccal oxycodone with paracetamol (n=34) and buccal fentanyl (n=38).	IIA
Fentanyl	OM	**Pietsch et al. 2023**[48] An observational study in 177 patients treated with OM fentanyl in prehospital trauma in ski and bike resorts. OM fentanyl significantly reduced pain from baseline by a median of NRS 3 (IQR 2 to 4) $p<0.0001$. Regression analysis indicated that the absolute reduction in pain but there was no difference observed because of age or gender, and no major adverse events were observed.	III

Therapy	Route of administration	Overview of study/data	Level of evidence
Sufentanil	SL	**Melson et al. 2014**[49] (*)Patients undergoing major elective surgery were randomised to a hand-held PCA device dispensing sufentanil SL tablets with a 20-minute lockout (n=177) or IV PCA morphine with a 6-minute lockout (n=180) for the treatment of acute postoperative pain. Successful analgesia (according to Patient Global Assessment) was achieved in 78.5% of patients receiving sufentanil and 65.6% of those receiving morphine.	IIB
Sufentanil	SL	**Meijer et al. 2018**[50] (*)A hand-held PCA device dispensing sufentanil SL tablets (with a lockout period of 20 minutes) was used for postoperative pain relief in 280 patients undergoing major surgery. SL sufentanil use provided effective analgesia in 90% of patients, with NRS scores <4 in 75% of patients. Over 70% of patients were highly satisfied with the system.	III
Sufentanil	SL	**Miner et al. 2018**[51] Patients presenting at the ED with pain ≥4 on the NRS due to trauma or injury received either a single (n=40) or multiple (n=36) doses (up to 3 additional doses at least 60 minutes apart) of SL sufentanil 30 µg. In both groups, reduction in pain was clinically meaningful within 30 minutes, and pain levels had dropped by 36% at 60 minutes. 75% of patients in the multiple dose cohort required only one dose of sufentanil in total.	III
Sufentanil	SL	**Miner et al. 2019**[52] Pooled safety study for Phase 3 studies of SL sufentanil for short-term treatment of moderate-to-severe acute pain in 804 patients. AEs were experienced by 60.5% (SL sufentanil) and 61.4% (placebo) and treatment-related AEs were experienced by 43.8% (SL sufentanil) and 33.5% (placebo) (10.3% difference; 95% CI: 2.0–18.6) of patients. Differences were significant for treatment-related AEs but not for AEs overall. Across all studies, nausea, which occurred in 34.1% of patients receiving SL sufentanil, was the only moderate AE that occurred in >5% of patients. Findings from the pooled analysis support that SL sufentanil is well tolerated, with most AEs considered mild or moderate in severity, for the treatment of moderate-to-severe acute pain in medically supervised settings.	III
Sufentanil	SL	**McWilliams et al. 2024**[53] Retrospective case analysis from the pre-hospital setting in search and rescue scenarios. Sixty-four cases were included in the analysis and demonstrated that mean pain score reduced from 8.0 ± 1.9 before sufentanil administration to 5.5 ± 2.5 after, reflecting a statistically significant difference of 2.6 ± 2.1 ($p < 0.001$). The results also revealed statistically significant reductions in HR and SBP following SL sufentanil administration (mean HR dropped by 4.2 ± 9.1 beats/min, p=0.004, and mean SBP dropped by 11.1 ± 21.8 mmHg, p=0.01). Changes in vital signs, although statistically significant, were not clinically significant and did not necessitate additional monitoring or intervention in any patients. This study suggests that SL sufentanil can provide significant reductions in pain with a favourable effect on vital signs.	III
Fentanyl	IN	**Borland et al. 2011**[54] An RCT performed in a children's hospital ED randomised paediatric patients aged 3 to 15 years with fractures to standard (n=98) or high concentration (n=91) IN fentanyl. There was no statistically significant difference in median pain score between the 2 groups at any of the study time points. Within groups, patients in the standard concentration group with weight <50 kg had a significantly greater reduction in pain score than those weighing ≥50 kg. There was no significant difference by weight group within the high concentration arm.	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
Sufentanil	IN	**Stephen et al. 2012[55]** IN sufentanil was given to 15 ED patients with acute extremity injuries. Over 30 minutes, mean pain score decreased by 4.3 points and 8 patients achieved a final pain score of ≤3. Average patient satisfaction was 4.5 out of 5.	III
Sufentanil	IN	**Steenblik et al. 2012[56]** Patients presenting with acute extremity injuries (most commonly upper extremity dislocations) to a ski resort clinic (n=40) were given IN sufentanil. Mean reduction in pain score was 4.7 at 10 minutes and 5.7 at 30 minutes. Five patients (12.5%) required more than 1 dose of sufentanil, and 78% of patients were very satisfied with their treatment.	III
Fentanyl	IN vs. SC	**Tanguay et al. 2020[57]** Retrospective chart analysis of IN fentanyl compared with SC fentanyl in patients (aged ≥14 years) with acute severe pain in the pre-hospital setting, and a subgroup analysis of patients aged ≤70 years and ≥70 years performed. 82.7% of patients had complete data (IN fentanyl 84.0%, SC fentanyl 81.2%). No difference was observed in time to administration or in the effectiveness of IN fentanyl and SC fentanyl, and neither route of administration resulted in major adverse events that required intervention. Subgroup analysis of IN fentanyl patients demonstrated that patients aged ≥70 years were more likely to experience pain relief compared to those <70 years. IN fentanyl was shown to be effective in all patients and potentially more effective in older patients.	III
Sufentanil	IN	**Kreps et al. 2021[58]** Observational, open-label sequential study in the ED in severe non-visceral pain. Control patients received SoC opioids and the intervention group received IN sufentanil. Pain at baseline was not comparable between groups (IN sufentanil AVPS score 8.5 [IQR 8.0–10.0] vs SoC 7.9 [IQR 7.0–9.4], p=0.026), but pain reduction was larger for those receiving sufentanil after 15 minutes: 2.5 vs 1.6 p=0.005 and remained significant at 30 minutes (AVPS 4 vs 3.1, p=0.02). After 30 minutes no difference in pain score was noted. No side effects were recorded with SoC but were reported by 62 sufentanil patients (68.1%). The most common AEs were vertigo (60.4%), nausea (30.0%) and vomiting (20.0%). Significantly fewer patients on SoC received rescue analgesia (4.3%) versus those on sufentanil (10.1%) (p=0.018).	IIA
Fentanyl	IN	**Anderson et al. 2022[59]** Single centre, retrospective chart review of initial dose 30 µg IN fentanyl rising to 102–265 µg based on pain (n=3,205). Fentanyl provided effective analgesia and was well tolerated even at doses >100 µg.	IIB
Sufentanil	IN	**Hutchings et al. 2023[60]** Systematic review of 4 studies, three in the ED and one in the pre-hospital setting of 467 patients were included. Primary outcome was pain reduction and secondary endpoints were AEs, rescue analgesia, and patient and provider satisfaction. Efficacy was determined by the percentage of patients achieving a reduction in pain to NRS ≤3/10. In a placebo-controlled study, IN sufentanil was superior to placebo for pain reduction at 30 minutes with 20.8% of patients achieving NRS <3 (95% CI 4.0–36.2%, p=0.01). In two studies IN sufentanil was comparable with IV morphine (0.1 mg/kg) and in the pre-hospital study a loading dose of IV sufentanil followed by smaller rescue doses was comparable with IV morphine. Mild AEs were common in all studies but sedation was noted more often with sufentanil.	IC

Therapy	Route of administration	Overview of study/data	Level of evidence
Sufentanil	IN	**Malinverni et al. 2024[61]** Single-centre, open-label, randomised, controlled, parallel-group study of trauma patients the ED with trauma pain ≥7 in receipt of IN sufentanil plus oral/IV paracetamol or IV opioids plus oral/IV paracetamol. Primary endpoint was change in VAS from baseline at 15–20 minutes. Secondary outcomes included between-group differences in mean VAS scores at 60 minutes and the proportion of patients experiencing side effects. The minimum clinically important difference was defined, as a change of 1 on the VAS. Additional outcomes include the use of rescue analgesia. Pain reduced over time in both groups but was significantly greater in the IN sufentanil group (VAS reduction 3.0, [IQR 1.7–5.0] vs 1.5 [IQR 0.9–3.0]; p<0.001). VAS pain score was statistically significantly lower in the sufentanil group (5.0 [IQR 3.0–7.0] vs 6.6 [IQR 5.0–73]; p=0.002). Onset to pain relief was faster for sufentanil. Statistically lower pain scores remained at 60 minutes (p<0.001). There was no change in the use of oral/IV paracetamol in either group, and the rate of rescue analgesia was similar (sufentanil 24.1% vs 23.0%; p=NS). Adverse events were more common in the sufentanil group (71.1% vs 23.0%; p<0.001), similarly the rate of SAEs in the sufentanil group were higher but this was not significant.	IIA
Fentanyl	IN	**Serra et al. 2023[62]** Systematic review of IN fentanyl in children (n=18 studies), adults (n=5), older people (n=1) in both ED and pre-hospital settings. In children IN fentanyl was equally effective to comparators, delayed the time to IV opioids, reduced ED length of stay and hospital admission rates. Patient satisfaction was generally comparable in all studies, but in one was suggested to be higher than IM morphine. In adults, IN fentanyl was comparable with SC fentanyl and IV morphine, but one study suggested IN fentanyl was less effective than IV fentanyl. Time to onset of analgesia was comparable between IN fentanyl and IV morphine but a higher dose of IN fentanyl was required. Patient satisfaction results indicated in one study no difference between IN or IV fentanyl in patients rating of satisfaction, however when compared with IN ketamine, IN fentanyl was judged to provide more satisfactory analgesia. AEs including hypoxia, sedation, bradycardia were reported with IN fentanyl but these were considered transient and minor.	IC
Sufentanil	IV	**Bounes et al. 2010[63]** Patients with acute severe trauma pain were randomised to IV sufentanil (n=54) or IV morphine (n=54). At 15 minutes, 74% of patients in the sufentanil group achieved pain relief (defined as NRS ≤3) versus 70% of those in the morphine group. Duration of analgesia was longer in the morphine group.	IIB
Morphine	IV	**Birnbaum et al. 2012[64]** In an RCT, patients in the ED with acute abdominal pain received an initial dose of IV morphine followed by physician-managed analgesia as needed. Patients randomised to PCA dosing also received either 1 mg (n=69) or 1.5 mg (n=72) morphine on demand with a 6 minute lockout between doses, while the non-PCA arm (n=70) did not. All 3 groups had similar, significant reductions in NRS scores to 30 minutes, after which NRS scores in the PCA groups continued to decline (to 120 minutes) while those in the non-PCA group did not (p=0.004).	IIA
Morphine	IV	**Rahman et al. 2012[65]** Patients with acute pain presenting to two EDs were randomised to morphine given either via PCA (n=24) or as titrated boluses (n=23). Patients in the PCA group had a significantly greater reduction in pain on the VAS than the bolus group (p<0.001), with similar consumption of morphine.	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
Morphine	IV	**Rahman et al. 2012[66]** In an RCT, patients with acute traumatic pain of VAS score ≥7 presenting to the ED were randomised to morphine given either via PCA (n=47) or as titrated boluses (n=49). Patients in the PCA group had lower mean VAS scores than the bolus group at all time points, and were more satisfied with their care.	IIA
Morphine	IV	**Farsi et al. 2013[67]** In an RCT in patients with limb trauma in the ED, IV morphine (n=100) or placebo (n=100) was given 30 minutes after an initial dose of IV morphine. Patients in the morphine arm had significantly reduced pain at 1 hour compared with placebo (p<0.05), with no significant difference in the rate of AEs.	IIA
Fentanyl	IV	**Wenderoth et al. 2013[68]** In a retrospective cohort study of IV fentanyl versus IV morphine, 168 patients with trauma pain in the ED achieved similar analgesia regardless of receipt of fentanyl or morphine (a reduction of NRS 2, [p=NS]). Baseline pain score in the IV fentanyl group was higher (NRS 10, IQR 8–10)) than IV morphine treated patients (NRS 8, IQR 4–10). Time to lowest pain score was faster with IV fentanyl (22 vs 47 minutes; p<0.001). Adverse event profiles in both groups were comparable, although the use of prophylactic anti-emetics was significantly higher in morphine treated patients (21.4% vs 0%; p<0.001).	III
Fentanyl	IV	**Farahmand et al. 2014[69]** In an RCT comparing nebulised fentanyl (n=47) with IV morphine (n=43) in ED patients with moderate-to-severe acute limb pain, fentanyl and morphine provided similar reductions in pain of >3 points on the NRS. Patient satisfaction in both groups was similar and no adverse effects were reported in the fentanyl group.	IIA
Fentanyl	IV	**Friesgaard et al. 2016[70]** Of 2,348 patients treated with IV fentanyl in a pre-hospital setting, 79.3% achieved pain reductions of NRS >2, but moderate-to-severe pain was still reported by 60% of patients on arrival at hospital.	III
Mixed opioids	IV	**Dalton et al. 2022[71]** Using a database 267,281 of 3,831 patients, 7% (n=768) were treated with opioids in the pre-hospital setting. Fentanyl was the most used opioid (88.2%) and median dose was 10 morphine equivalents. Patients who received opioids had higher baseline pain than those not receiving opioids (9 versus 4, p<0.001) and experienced a median reduction in pain score of 3 points. AEs were rare and included altered mental status and respiratory compromise.	III
Morphine	IV	**Oon et al. 2024[72]** SLR and meta-analysis of 8 trials (n=1490) comparing PCA and IV morphine. Pain was comparably reduced by both approaches (treatment difference −0.2, p=0.25), and there were no differences in dosages used to reduce pain. Overall, more patients were satisfied with PCA than IV (p<0.001) and fewer patients on PCA required rescue analgesia (p<0.001). Reporting of AEs in the studies included was too limited to draw firm conclusions.	IA
Fentanyl, morphine and alfentanil	IV, oral, intraosseous	**Colding-Jørgensen et al. 2025[73]** Registry based study in Denmark exploring the use of strong opioids (morphine, fentanyl and alfentanil) in children in the pre-hospital setting. Fentanyl was the most administered opioid (96.4% of 1,700 patients). The IV route was used in 63.4% of cases and 97% of all doses provided to patients were within recommended dosing ranges. Only 5.7% of all children aged <15 years received opioids and 75% of these were aged >10 years and only 8.5% of patients were aged <5 years. These data suggest a potential for under-treatment of pain in children.	III

Therapy	Route of administration	Overview of study/data	Level of evidence
KETAMINE			
	Oral	**Gerges et al. 2022**[74] Prospective, randomised, open-label trial in 60 patients aged >18 years with acute moderate-to-severe MSK pain and initial NRS score of ≥5. Patients received either aspirin 324 mg or 0.5 mg/kg oral ketamine. Pain was measured at 30, 60, 90 and 120 minutes. Primary endpoint was change in pain at 60 minutes. At 60 minutes mean change in pain score (measured by NRS) for aspirin was 2.1 (8.4 to 6.3, 95% CI 1.35–3.00) and oral ketamine 4.1 (7.8 to 3.7, 95% CI 3.25–4.90). No serious AEs occurred in either group, or clinically relevant change in vital signs observed. No patients required rescue medication at 60 minutes. The most common AEs reported were dizziness and fatigue.	III
	IN	**Shimonovichh et al 2016**[75] Patients in the ED with moderate-to-severe acute traumatic pain were randomised to IN ketamine (n=34), IV morphine (n=26) or IM morphine (n=30). Pain relief 1 hour after treatment was significant and comparable between groups. IN ketamine was clinically comparable to IV morphine in terms of time to onset (14.3 versus 8.9 minutes) and time to maximum pain reduction (40.4 versus 33.4 minutes).	IIA
	IN vs IV	**Parvizrad et al. 2017**[76] In an RCT comparing IN ketamine (n=77) with IV ketamine (n=77) in patients with orthopaedic trauma, IN ketamine was found to be as effective as IV ketamine in reducing pain at 30 minutes. Rescue analgesia was required in 20% of patients (with no difference between groups). Adverse events were mild and transient in both groups.	IB
	IN	**Farnia et al. 2017**[77] Patients with renal colic (n=40) received IV morphine (n=20) or IN ketamine (n=20) in a double-blind RCT. At baseline pain scores were higher in the morphine group vs that in the ketamine group (VAS: morphine 7.40 ± 1.18; ketamine 8.35 ± 1.30) (p=0.021). At 5 minutes post-administration, pain relief with morphine was superior to ketamine, VAS scores were 6.07 ± 0.47 for morphine and 6.87 ± 0.47 for ketamine (p=0.025). At 15 minutes and 30 minutes, pain scores for both groups were comparable. At 15 minutes: morphine 5.24 ± 0.49 morphine, ketamine 5.60 ± 0.49, mean difference –0.36; at 30 minutes: morphine 4.02 ± 0.59, ketamine 4.17 ± 0.59, mean difference –0.15.	IB
	IN	**Reynolds et al. 2017**[78] Children aged 4 to 17 years with suspected extremity fractures were randomised to IN ketamine (n=43) or IN fentanyl (n=44). Similar pain relief was observed at 20 minutes between groups, with both groups requiring a similar level of opioid rescue therapy (16% versus 18%).	IB
	IN	**Frey et al. 2018**[79] Children aged 8 to 17 years presenting to the ED with moderate-to-severe pain due to traumatic limb injuries were randomised to either IN ketamine (n=45) or IN fentanyl (n=45). After 30 minutes pain reduction was comparable between groups (−30.6 and −31.9 mm on 100 mm VAS). The need for rescue analgesia was similar between groups.	IB

Therapy	Route of administration	Overview of study/data	Level of evidence
	IN	**Li et al. 2021[80]** SLR of seven studies of IN ketamine versus opioids for acute pain management in ED at 15, 30 and 60 minutes. Comparisons included: • IN ketamine vs placebo (3 studies) • IN ketamine vs opioids (4 studies) Meta-analysis of the included studies demonstrated a tendency towards better pain relief with IN ketamine compared with placebo at 15 minutes (mean difference −0.90 95% CI: −2.34, 0.54 I^2=94% p=0.22) and 60 minutes (mean difference: −1.47 95% CI: −3.04, 0.10 I^2=71% p=0.07). The need for rescue medication was significantly lower for IN ketamine than placebo (OR: 0.36 95% CI: 0.16, 0.80 I^2=66% p=0.01). Meta-analysis of the included studies demonstrated a tendency towards better pain relief with IN ketamine compared with placebo (mean difference −0.90 95% CI: −2.34, 0.54 I^2=94% p=0.22) and 60 minutes (mean difference: −1.47 95% CI: −3.04, 0.10 I^2=71% p=0.07). The need for rescue medication was significantly lower for IN ketamine than placebo (OR: 0.36 95% CI: 0.16, 0.80 I^2=66% p=0.01). Compared with opioids, IN ketamine had comparable AEs, but significantly more AEs i.e. dizziness than those reported by placebo-treated patients (OR: 1.84 95% CI: 1.35, 2.51 I^2=0% p=0.001). Compared with opioids there was no significant difference in pain relief at 154 minutes, but IN ketamine provided better pain reduction at 30 minutes (p=0.04). One study reported pain scores at 60 minutes with no difference in efficacy. Meta-analysis of studies of IN ketamine versus opioids showed that IN ketamine significantly reduced pain (mean difference: −0.82 95% CI: −1.43, −0.20 I^2=64% p=0.009). The need for rescue medication was higher for IN ketamine than opioids (OR: 4.69 95% CI: 1.75, 12.60 I^2=not applicable p=0.02). AEs with IN ketamine were similar to that with opioids with no difference in the incidence of dizziness (OR: 1.78 95% CI: 0.54, 5.93 I^2=43% p=0.34) and nausea/vomiting (OR: 1.47 95% CI: 0.67, 3.20 I^2=0% p=0.33). IN ketamine had comparable AEs, but with significantly increased incidence of dizziness, than those reported by placebo-treated patients (OR: 1.84 95% CI: 1.35, 2.51 I^2=0% p=0.001). Emergent AEs were significantly increased with IN ketamine as compared to opioids and placebo.	IC
	IN	**Seak et al. 2021[81]** SLR and meta-analysis of 7 studies (of high or moderate quality) including 1,760 patients in receipt of IN ketamine with IV analgesics or placebo. Pain scores were comparable between patients receiving IN ketamine or IV analgesics (morphine or fentanyl) with no significant difference in pain score at any time points 5 minutes (mean difference 0.94, p=NS), 15 minutes (mean difference 0.15, p=NS), 25 minutes (mean difference 0.24, p=NS), 30 and 60 minutes (mean difference at 30 minutes −0.05, p=NS; 60 minutes mean difference −0.42, p=NS). There was no significant differences in the need for rescue analgesia between ketamine and opioids. Only mild AEs were observed in those who received IN ketamine, but patients experienced an increased risk of dizziness (OR 1.9 95% CI 1.4–2.5; p<0.0001) difficulty concentrating (OR 5.3 95% CI 1.5–19.0; p=0.01), confusion (OR 7.0 95% CI 1.6–29.9; p=0.009) or disorientation (OR 9.2 95% CI 3.6-23.4; p<0.00001) compared with control groups. IN ketamine was non-inferior to IV analgesics.	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
	IN	**Tongbua et al. 2022**[82] Double-blind, randomised controlled trial of patients aged >65 years in the ED with acute moderate-to-severe MSK pain (NRS ≥5) randomised to IN ketamine or IV morphine. Mean (±SD) baseline pain scores were similar in IN ketamine and IV morphine groups (8.16 ± 1.68 versus 7.62 ± 1.85, p>0.05). After 30 minutes, mean (±SD) pain scores were reduced in both groups to 6.03 ± 1.68 and 5.81 ± 2.76, respectively. The mean difference at 30 minutes was not significant (0.22, 95% CI: −1.04 to 1.48). Patients randomised to IN ketamine (n=37) or IV morphine (n=37) achieved comparable pain relief at 30 minutes (NRS 6.03 vs 5.81), and NRS change from baseline was −2.14 (95% CI −2.79 to −1.48) for IN ketamine and −0.81 (95% CI −3.26 to −1.26) for IV morphine and the mean difference (−0.32, 95% CI: −1.17 to 0.52) did not exceed the margin for non-inferiority (upper limit of 95% CI <1.3). There was no difference in rescue analgesia requirements between IN ketamine and IV morphine groups, and no difference in dizziness or vomiting.	IIB
	Nebulised	**Drapkin et al. 2020**[83] Case series in 5 adults of nebulised ketamine in the ED. Three patients received 1.5 mg/kg, one received 1 mg/kg and one received 0.75 mg/kg. All patients experienced a decrease in pain up to 120 minutes and no AEs were reported.	IV
	Nebulised	**Rhodes et al. 2021**[84] Case series of nebulised ketamine in children aged 10–16 years (n=5) with a mix of MSK pain including fracture and joint effusion. All patients experienced a reduction in pain from 15 minutes, which was maintained up to 60 minutes. No change in baseline vitals was observed and four of the five patients experienced dizziness that resolved by 60 minutes.	III
	Nebulised	**Dove et al. 2021**[85] Prospective, randomised, double-blind trial. Patients (n=120) in the ED were randomised to 3 doses of nebulised ketamine (0.75 mg/kg, 1 mg/kg and 1.5 mg/kg) and NRS pain score measured at 30 minutes. At 30 minutes the reduction in pain score was comparable across all groups with all experiencing a reduction in pain score >1.3. Reductions in pain score were: • 0.75 mg/kg: 8.7 at baseline to 4.7 at 30 minutes and 3.7 at 120 minutes • 1 mg/kg: 8.6 at baseline to 4.4 at 30 minutes and 3.4 at 120 minutes • 1.5 mg/kg: 8.7 at baseline to 4.6 at 30 minutes and 3.6 at 120 minutes. Ketamine was effective at all doses tested, up to 120 minutes.	IIB

Therapy	Route of administration	Overview of study/data	Level of evidence
	Nebulised vs IV	**Nguyen et al. 2024**[86] Prospective, randomised, double-blind, double-dummy in one ED of IV ketamine in adult patients (aged ≥18 years) with a NRS score of ≥5. Patients received single dose of nebulised ketamine 0.75 mg/kg or IV ketamine 0.3 mg/kg. Primary study outcome was differences in NRS at 30 minutes. Secondary outcomes were rescue analgesia, AEs, and pain scores at 15, 30, 60, 90 and 120 minutes. Minimum clinically important difference was designated as 1.3 points. Baseline pain scores in the nebulised (n=75) or IV ketamine group (n=75) were comparable. Pain reduction from 8.2 to 3.6 for those receiving nebulised ketamine and 8.2 to 3.8 for IV ketamine was observed (mean treatment difference 0.23 [95% CI −1.32–0.86]). No significant differences in pain reduction between the two groups was observed at any other timepoint. No clinical concerning changes in vital signs were observed in any patients, and no SAEs were noted. But more subjects in the IV group experienced sedation, restlessness, dizziness and feelings of unreality. There was no difference in rescue analgesia requirements.	IIA
	Nebulised	**Cetin et al. 2025**[87] SLR and meta-analysis of nebulised ketamine in the ED. Thirteen studies met the criteria for inclusion. In 8 studies nebulised ketamine was comparable with active controls, and in 4 studies ketamine was comparable with IV morphine at 30 minutes with similar rates of rescue analgesia required 16.9% versus 17.4%. Most studies (11/13) reported no difference in AEs (39.1% versus 37.8%) and no reports of serious AEs. Nebulised ketamine is comparable to morphine, but the level of confidence in the meta-analysis was low.	IA
	IV	**Jennings et al. 2012**[88] Patients with pain due to trauma in the pre-hospital setting were randomised in an open-label study to morphine or morphine plus ketamine. All patients received IV morphine 5 mg, and were then randomised to ketamine (mean total dose 40.6 ± 25 mg) or morphine (mean total dose 14.4 ± 9.4 mg). Mean change in pain score from baseline was –5.6 (95% CI –6.2 to –5.0) for ketamine and –2.4 (95% CI –3.7 to –2.7) for morphine. AEs were more commonly reported in patients treated with ketamine (n=27/70, 39%), the most common of which was disorientation, vs morphine (n=9/65, 14%), the most common of which was nausea.	IIA
	IV	**Majidinejad et al. 2014**[89] Patients with long bone fractures were randomised to IV morphine (n=63) or low-dose IV ketamine (n=63). Pain scores decreased significantly in both groups at 10 minutes, with no significant differences between groups.	IIB
	IV	**Miller et al 2015**[90] An RCT of patients with acute pain in the ED compared low-dose IV ketamine (n=24) with IV morphine (n=21). There were no significant differences in NRS reduction between groups at any time point. Time to achieve maximum NRS reduction was 5 minutes for ketamine and 100 minutes for morphine.	IB

Therapy	Route of administration	Overview of study/data	Level of evidence
	IV and IN	**Sandberg et al. 2020[91]** Systematic review exploring ketamine (range of administration routes) versus opioids when given alone and when administered in combination with nitrous oxide. Studies covered 5 comparisons • IV ketamine vs IV opioids (three studies) • IV ketamine plus IV morphine vs IV morphine (three studies) • IV ketamine as an infusion vs IV ketamine single dose (one study) • IN ketamine plus nitrous oxide vs nitrous oxide alone (one study) • IV ketamine vs no analgesia. Most studies (n=5/8) were noted to contain high levels of bias. In studies of ketamine versus opioids, ketamine provided a greater reduction in pain score than morphine or fentanyl but was comparable with pentazocine. In these studies, fewer patients treated with ketamine experienced AEs of nausea and vomiting, and fewer patients treated with opioids experienced agitation. Ketamine plus morphine versus morphine only showed lower pain scores in the combination group versus morphine alone, but a meta-analysis done by these authors indicated the difference was not significant. AEs were broadly comparable, but there was a trend towards fewer AEs with morphine alone. Continuous IV ketamine infusions compared with a single bolus dose of ketamine in patients also receiving morphine demonstrated comparable pain relief. IN ketamine plus nitrous oxide versus nitrous oxide alone showed superior pain relief in the combination group with a NRS pain reduction of 2 or more, with no serious AEs reported. Compared with no analgesia in a warzone, ketamine was superior to no analgesia but this was not significant. There was inconsistent reporting across studies, with imprecision in results and lack of randomisation, but it was considered that IV ketamine was at least as effective as opioids.	IC
	IV	**Lovett et al. 2021[92]** Randomised, prospective, double-blind non-inferiority study in patients aged 18–59 years with acute moderate-to-severe pain in the ED treated with IV ketamine 0.15 mg/kg or 0.3 mg/kg. The primary endpoint was the 11-point NRS pain score between groups at 30 minutes. Secondary endpoints included NRS pain scores at 15 and 60 minutes; change in NRS at 15, 30, and 60 minutes; rescue analgesia; and adverse effects. Forty-nine patients were randomised to 0.15 mg/kg and 0.3 mg/kg respectively. Mean baseline NRS score at 30 minutes post-intervention for ketamine 0.15 mg/kg was 4.7 (95% CI 3.8–5.5) and 5.0 in the 0.3 mg/kg group (95% CI = 4.2–5.8); (mean difference = 0.4, 95% CI = −0.8 to 1.5). Data indicate that ketamine 0.15 mg/kg was non-inferior to 0.3 mg/kg (lower limit of 95% CI = −0.8 to ≥1.3). Adverse effects were similar at 30 minutes. At 15 minutes, the 0.3 mg/kg group experienced greater change in NRS; however, more adverse effects occurred.	IB
	IV	**Balzer et al. 2021[93]** SLR and meta-analysis of 8 RCTs in 1,191 patients explored low-dose IV ketamine against IV morphine. At 60 minutes there was no difference in mean pain score, but there was a trend favouring morphine between 60 minutes and 120 minutes. The requirement for rescue medication was comparable in both groups (RR 0.97; 95% CI 0.5 to 3.16) and the rate of AEs was comparable between both groups.	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
	IV	**Esfahani et al. 2021**[94] Seventy three patients were enrolled and 36 allocated to ketamine and 37 allocated to morphine – baseline characteristics were comparable in both groups. Mean pain score changed −6.2 (95% CI −5.72 to −6.69) for those receiving ketamine versus −5.8 (95% CI −5.15 to −6.48) for morphine. At all timepoints mean pain score was lower in those receiving ketamine versus morphine (p<0.05), and the mean total pain reduction was greater with ketamine than morphine (p=0.002). This study suggested that low doses of ketamine are as effective in managing pain than morphine for those with lower limb trauma.	IA
	IV	**Moradi et al. 2022**[95] Single-centre randomised ED clinical trial in 200 patients with acute pain who received ketamine plus haloperidol or fentanyl as analgesia. Primary endpoint was pain score at baseline and post-administration and safety. There was no significant difference between the mean scores of initial pain in the two groups, but at all intervals of 5, 10, 15 and 30 minutes after injection, the mean of pain scores of patients in the group receiving ketamine plus haloperidol were lower. The need for injection of rescue analgesic was 9% in the ketamine plus haloperidol group and 34% in the fentanyl group. The mean agitation score did not differ between the two groups except at 10 minutes when agitation was higher in those receiving ketamine.	IIB
	IV	**Beaudrie-Nunn et al. 2023**[96] Doses of ketamine <0.3 mg/kg and >0.3 mg/kg were compared in a multi-centre, retrospective cohort study in 21 EDs in 3,796 patients. Median baseline pain score in the low dose group (n=258) was NRS 8.2 and NRS 7.8 in the high-dose group (n=126). Both groups had significant reductions in pain score within 60 minutes of administration but there was no significant difference between the two groups. AEs were comparable between groups with the most common AEs being agitation (7.3%) and nausea (7.0%).	IA
	IV and IN	**Shi et al. 2024**[97] Twenty-six studies were included in a meta-analysis to evaluate IV or IN ketamine with pain reduction evaluated at 15, 30, 45 and 60 minutes. At early timepoints (15 and 30 minutes) ketamine provided more effective pain relief than comparators (morphine and fentanyl) but this was not significant. At 60 minutes there was no difference in pain relief between ketamine and comparators. The most common dosage of ketamine was 0.3 mg/kg. There was no significant difference in the requirement for rescue analgesia in any treatment group and AEs were broadly comparable across groups. The authors noted that many studies had a high risk of bias, but pain relief within 30 minutes was clinically meaningful with an optimal dose of 0.3 mg/kg. Beyond 30 minutes the analgesia provided by ketamine was comparable to other analgesics.	IC
	IV/IN	**Guo et al. 2024**[98] This meta-analysis of 15 RCTs involving 1,768 patients compared IV/IN ketamine with IV morphine. Primary outcome measures were pain scores (NRS and VAS) with secondary endpoints of complete resolution of pain, reduction in pain of NRS ≥3 points or reductions in NRS of ≥50 or 60%, change in NRS score, change in VAS score, rescue medication, adverse events and patient satisfaction. At 30 minutes, patients treated with ketamine had lower NRS pain scores than those treated with morphine (p<0.00001) but morphine was superior at 120 minutes (p=0.0003). Complete resolution of pain was observed in three times more patients in the ketamine group at 15 minutes than morphine (RR 3.18 95% CI 1.75–5.78, p=0.0001). Ketamine treatment was associated with fewer AEs than morphine (RR 0.34 95% CI 0.18–0.66, p=0.001).	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
	IV	**Azizkhani et al. 2025[99]** Double-blind, randomised study in two ED settings, in patients aged >18 with acute onset, moderate pain randomised to receive IV ketamine at two doses in 80 patients. Patients received either 0.3 mg/kg ketamine over 1 minute followed by an infusion of placebo over 30 minutes or ketamine bolus 0.15 mg/kg followed by ketamine infusion 0.15 mg/kg over 30 minutes. Primary outcome measures was median decrease in NRS, levels of sedation, changes in vital signs and AEs. All groups experienced a significant reduction in pain at 30 minutes ($p<0.001$), with pain scores lower in the ketamine bolus plus infusion groups (p=NS). Vital signs and AEs were comparable in both groups. No impact on vital signs was observed in both groups, apart from a comparable increase in blood pressure. Patients in the infusion group required less rescue analgesia but this was not significantly different between groups. The most common side effects were feelings of unreality, hallucination, agitation, and nausea. No statistically significant difference was observed between study groups in any side effect including the mean agitation or sedation as measured by the RASS scale.	IB
	IV	**Moradi et al. 2025[100]** A single-centre, randomised controlled trial of 258 adult patients in the ED with acute limb trauma pain. One group received IV ketamine (0.3 mg/kg) plus dexmedetomidine (0.5 mcg/kg), and the other group IV morphine (0.1 mg/kg). Pain, agitation scores and side effects were compared between the two groups. Primary outcome was pain reduction at 30 minutes. At baseline mean pain score was 8.51 (ketamine plus dexmedetomidine 8.5 ± 1.4; morphine 8.4 ± 1.4). After 30 minutes post-administration mean pain score of patients in the ketamine-dexmedetomidine group was lower than the morphine group (ketamine plus dexmedetomidine: 1.4 ± 2.3 vs morphine: 3.3 ± 2.3, $p<0.001$). The need for rescue analgesic was 8.3% in the ketamine-dexmedetomidine group and 24% in the morphine group. The mean agitation score in the ketamine group was higher during the first 10 minutes post-injection (ketamine-dexmedetomidine 0.1 ± 0.6, p=0.052 vs morphine 0.0 ± 0.2, p=0.002) but this was resolved by 30 minutes (ketamine-dexmedetomidine 0.0 ± 0.3, p=0.007 vs morphine 0.0 ± 0.2, p=0.006).	IB
	Mixed (IV, IN, nebulised)	**Alanazi et al. 2022[101]** SLR of four RCTS of ketamine versus opioids (morphine and fentanyl) for severe pain in children. Ketamine was non-inferior to opioids determined by patient self-report pain assessment.	IC
	Mixed	**Fjendbo Galili et al. 2023[102]** Evaluation of sub-dissociative single-dose ketamine (routes of administration vary) trials (n=8) evaluated in SLR and meta-analysis included (n=903). Studies were judged to be at moderate to high risk of bias. Mean pain intensity scores were significantly lower 60 minutes after study drug administration favouring adjuvant ketamine (mean difference −0.76; 95% CI −1.19 to −0.33), compared with opioids alone. There was no evidence of differences in mean pain intensity scores at any other time point. Patients who received adjuvant ketamine were less likely to require rescue analgesia, no more likely to experience serious side effects and had higher satisfaction scores, compared with opioids alone. Thes data indicate effective pain reduction with ketamine that is comparable with opioids.	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
METHOXYFLURANE			
	Inhaled	**Bendall et al. 2011**[103] In paediatric patients with moderate-to-severe acute pain in a pre-hospital setting, effective analgesia (defined as a reduction in NRS pain score of at least 30%) was achieved in 78.3%, 87.5% and 89.5% of patients given methoxyflurane, morphine and fentanyl, respectively.	III
	Inhaled	**Johnston et al. 2011**[104] In a retrospective observational study of 1,024 patients with visceral pain who received methoxyflurane (n=465), IN fentanyl (n=397) or both (n=162) in the pre-hospital setting, methoxyflurane provided more rapid onset of action than IN fentanyl (VAS 2.0 versus 1.6 at 5 minutes), although fentanyl provided greater pain reduction by arrival at hospital (3.2 versus 2.5).	III
	Inhaled	**Coffey et al. 2014**[105] In a Phase 3 study of patients presenting to the ED with minor trauma (including 90 individuals aged 12 to 17 years), those randomised to methoxyflurane (n=150) reported significantly greater reductions in pain severity at all time points tested than those randomised to placebo (n=150) (p<0.0001). Onset of pain relief occurred within 6 to 10 inhalations and the greatest treatment effect with methoxyflurane (of −18.5 mm) was seen at 15 minutes.	III
	Inhaled	**Coffey et al. 2016**[106] In the adult subgroup of the above Phase 3 study, mean change from baseline was greater for methoxyflurane than placebo at all time points (−34.8 versus −15.2 mm on 100 mm VAS at 20 minutes). Median time to first pain relief was 5 minutes, versus 20 minutes with placebo, and 79.4% of patients in the methoxyflurane arm experienced pain relief within 1 to 10 inhalations.	IIA
	Inhaled	**Mercadante et al. 2019**[107] Adult trauma patients treated with methoxyflurane (n=135) or SoC analgesia (n=135; NRS ≥4–6 IV paracetamol/IV ketoprofen; NRS ≥7 IV morphine) had a greater reductions in VAS over 10 minutes than SoC (ΔVAS −5.94 mm; 95% CI: −8.83 mm, −3.06 mm p<0.001). Over 10 minutes comparable results were observed in patients with moderate baseline pain (ΔVAS −5.97 mm; 95% CI: −9.55 mm, −2.39 mm p=0.001) where SoC was IV paracetamol or IV ketoprofen and severe baseline pain where patients received IV morphine (ΔVAS −5.54 mm; 95% CI: −10.49 mm, −0.59 mm p=0.029). Median time to onset of first pain relief was 9 minutes (95% CI, 7.2 minutes, 10.28 minutes) with methoxyflurane compared with 15 minutes (95% CI, 14.17 minutes, 15.83 minutes) for SoC.	IIA
	Inhaled	**Borobia et al. 2020**[108] In adult trauma patients treated with methoxyflurane (n=156) or SoC (n=149), change from baseline pain was greater over 20 minutes for methoxyflurane than SoC 2.5 points vs 1.4 points (p<0.001). Significant reductions in pain were demonstrated for methoxyflurane regardless of baseline pain, and pain reduction with methoxyflurane was greater than SoC even if SoC contained opioids. Onset to pain reduction was 3 minutes for methoxyflurane compared with 10 minutes for SoC (p<0.001).	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
	Inhaled	**Brichko et al. 2020[109]** Patients were randomised to SoC analgesia or methoxyflurane (n=120), primary outcome was 50% reduction in pain score by 30 minutes and secondary endpoints at multiple timepoints. At 30 minutes 6 patients (10%) in the methoxyflurane group and 3 (5%) in the SoC group achieved a 50% reduction in pain score (p=NS). Reduction in pain (NRS reduced by 2 points) was significant at all timepoints for those receiving methoxyflurane (p<0.001). Time to requirement for rescue analgesia was longer for methoxyflurane 66 minutes versus SoC 46 minutes (p=0.024). No serious AEs were recorded.	IA
	Inhaled	**Ricard-Hibon et al. 2020[110]** Randomised, prospective, double-blind, placebo-controlled, trial in eight EDs in adults with pain score NRS ≥4. Patients received either methoxyflurane plus SoC analgesia or SoC plus placebo. Primary outcome measure was time until pain relief ≤30 mm, assessed on the 100 mm VAS. A total of 351 patients were analysed (methoxyflurane plus SoC n=178; SoC plus placebo n=173). Median pain prior to first inhalation was 66 mm, 75% of patients had severe pain (NRS 6–10). Median time to pain relief was 35 minutes [95% confidence interval (CI), 28–62] for methoxyflurane plus SoC versus pain relief not reached in SoC plus placebo (> 92 minutes – last timepoint for evaluation) (HR, 1.93 [95% CI 1.43–2.60]; p < 0.001]. Pain relief was most pronounced in the severe pain subgroup with an NRS ≥6 (HR 2.5 [95% CI 1.7–3.7]). Patients received the following as SoC • No analgesia: 38% of methoxyflurane plus SoC patients versus 29% of SoC-treated patients (p=0.07) • Weak opioids: 6% of methoxyflurane plus SoC patients versus 8% of SoC-treated patients • Strong opioids: 1% of methoxyflurane plus SoC patients and 1% of SoC-treated patients • Escalation to weak or strong opioids: 8% of methoxyflurane plus SoC patients versus 17% of SoC-treated patients (p = 0.02). Most adverse events were of mild intensity (111/147 events). The most common AEs were dizziness, somnolence, cough and nausea. Methoxyflurane used as part of a multimodal analgesic approach was effective in providing pain relief for adult trauma patients, particularly in those with severe pain.	IA
	Inhaled	**Serra et al. 2020[111]** Sub-group post-hoc analysis of the MEDITA study methoxyflurane by Mercadante et al. 2019 in patients aged ≥65 years. All patients had NRS ≥4 and received methoxyflurane or SoC (IV paracetamol 1 g, or ketoprofen 100 mg [moderate pain NRS 4–6] or IV morphine 0.1 mg/kg [severe pain NRS ≥7]). Primary endpoint was overall change in VAS at 3, 5 and 10 minutes. Secondary endpoints were time to onset of pain relief, efficacy up to 30 minutes and safety. Pain reductions were similar regardless of treatment, but time to onset of pain relief was shorter with methoxyflurane (9 minutes vs 15 minutes for SoC). Patients were 5.7 times more likely to express satisfaction with methoxyflurane than SoC and satisfaction was 3.4 times more likely for clinicians. AEs were similar in all patients, all of which were non-serious and there were no changes in vital signs.	III

Therapy	Route of administration	Overview of study/data	Level of evidence
	Inhaled	**Young et al. 2020**[112] Service evaluation of methoxyflurane (n=79) versus those in receipt of SoC analgesia (n=80) evaluating length of stay in the ED. Mean time spent in the ED was reduced by 71 minutes for those treated with methoxyflurane compared with SoC (276 minutes vs 347 minutes) which was statistically significant (p=0.038). Results were maintained by injury type. For shoulder dislocation methoxyflurane significantly reduced length of stay in the ED (167 minutes vs 350 minutes p=0.009) and was lower than SoC for upper limb injury (273 minutes versus 345 minutes) but this was not statistically significant. There were no reported significant adverse events associated with methoxyflurane treatment and it was generally well tolerated.	III
	Inhaled	**Fabbri et al. 2021**[113] A meta-analysis using pooled data from RCTs demonstrated that pain intensity difference was significantly superior for methoxyflurane to SoC analgesia (treatment effect 11.88, 95% CI 9.75–14.00, p<0.0001). Onset to analgesic effect was rapid with superiority of analgesic effect observed at 5 minutes and this was maintained at all timepoints. Comparable results were also noted in elderly patients.	IA
	Inhaled	**Johansson et al. 2021**[114] Pre-hospital evaluation of 32 patients (16 male; 16 female) with on-scene NRS median pain score of 8 (IQR 7.25–10.0) reduced to NRS 5 (IQR 4.0–7.0 p=0.001) by arrival at hospital. Women had lower median pain scores than men (4.0 [IQR 3.76–6.0] vs 6.0 [IQR 5.0–7.25], p=0.036). On average patients required 2 inhalers and the average number of inhaled breaths to achieve pain relief was 17 ± 9. The authors indicate significantly lower pain scores for patients treated with methoxyflurane, but the study was limited by the diversity of patient population and aetiology of pain and its observational design.	III
	Inhaled	**Lim et al. 2021**[115] Randomised, crossover study (paramedic administration) of methoxyflurane and IM tramadol in patients aged ≥16 years with MSK trauma. Primary endpoint was reduction in NRS ≥3 within 20 minutes. At 5 minutes pain relief was greater with methoxyflurane compared with tramadol (NRS reduction 2.0 vs 1.0, p=0.001) which remained significant at 10 and 15 minutes (10 minutes: NRS reduction 3.0 vs 1.0, p=0.001; 15 minutes: 4.0 vs 1.0, p=0.001) and remained significant by 20 minutes (NRS reduction 4.0 vs 1.0, p=0.028). More patients treated with IM tramadol had a NRS reduction ≥3 (71.6%) versus methoxyflurane-treated patients (46.7%). Administration time was faster for methoxyflurane than IM tramadol (9 minutes vs 11 minutes p<0.001). AEs were more common with methoxyflurane 44.3% vs 6.3% (p<0.001) but were mostly mild. Patients treated with methoxyflurane had higher paramedic and patient satisfaction scores.	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
	Inhaled	**Siriwardena et al. 2021**[116] A non-randomised pre-hospital study in 483 patients. Verbal numerical pain scores (VNPS) were collected from all patients and compared with retrospective pain scores from a database in comparable patients. Methoxyflurane's time to achieve maximum pain relief was significantly faster (all p-values <0.001): 25.7 mins (95% CI 24.4–27.0) versus nitrous oxide 44.4 (39.5–49.3); 25.8 (24.5–27.1) versus IV paracetamol 40.7 (34.6–46.9); 25.7 (24.4–27.0) versus IV morphine 41.9 (38.9–44.8). Scenario analyses of time spent in severe pain (VNPS on administration scoring 10 reducing to a score of 7) were significantly less for methoxyflurane (all difference p-values <0.001): 7.6 mins (95% CI 6.5–8.7) versus nitrous oxide 24.6 (20.1–29.0); 6.7 (5.6–7.7) versus IV paracetamol 23.0 (17.9–28.0); 6.9 (5.9–7.9) versus IV morphine 14.9 (13.3–16.6). Modelling results included demonstration of statistically significant clinical effectiveness of methoxyflurane over each comparator (all p-values <0.001). Thirty-two patients reported side effects, 19 of whom discontinued early. Thirteen patients, 10 aged over 75 years, were non-adherent to instructions given on inhaler use.	III
	Inhaled	**Trimmel et al. 2022**[117] Observational study in adult trauma patients (e.g. dislocations, fracture or low back pain following minor trauma) with moderate-to-severe pain (NRS ≥4) receiving methoxyflurane for up to 30 minutes. Median numeric pain rating was 8.0 (7.0–8.0) in 109 patients. Sufficient analgesia (reduction of NRS ≥3) was achieved by inhaled methoxyflurane alone in 67 patients (61%). The analgesic effect was progressively better with increasing age. Side effects were frequent (n=58, 53%) but mild. User satisfaction was scored as very good when pain relief was sufficient, but fair in patients without benefit. Technical problems were observed in 16 cases (14.7%), mainly related to filling of the inhaler. In every fifth use, the fruity smell of methoxyflurane was experienced as unpleasant. No negative effects on vital signs were observed. This study indicates that methoxyflurane is appropriate and beneficial for pain relief when transporting patients to hospital.	III
	Inhaled	**Hyldmo et al. 2024**[118] Systematic review of inhaled analgesics including methoxyflurane or nitrous oxide. Seven studies (n=56,535 patients) compared methoxyflurane or nitrous oxide to placebo or other drugs. All evidence was judged to be of poor quality, many with a high risk of bias. Only one study involved nitrous oxide and pain reduction was moderate, but clinically important, compared with placebo. No significant difference was observed in AEs between nitrous oxide and placebo. For methoxyflurane, it was anticipated that onset to analgesia would be faster than IV analgesics because of the extended set-up time for IV administration. However, it was suggested that IV analgesics will have a longer duration of action. Reduction of pain judged as a reduction in NRS ≥3 was not apparent at 20 minutes with methoxyflurane. However, at timepoints longer than 20 minutes, the potential to reduce NRS by ≥3 was improved with 47% of patients reporting this reduction. The authors note however, that this reduction with longer duration of use, may reflect the use of a second methoxyflurane inhaler. Methoxyflurane was generally associated with a low rate of AEs, but it is unclear if these differ for pre-hospital or ED patients due to transport and evacuation. Methoxyflurane also appears to have an acceptable level of environmental contamination, but the authors noted many countries do not have set occupational limits.	IC

Therapy	Route of administration	Overview of study/data	Level of evidence
	Inhaled	**Kelty et al. 2024**[119] Retrospective cohort safety study in the pre-hospital setting using probabilistic data of 37,211 children. The cohort included 9,472 treated with methoxyflurane alone (25.5%), 1,235 (3.3%) treated with opioids alone and 23,740 (63.8%) treated with combined methoxyflurane and opioids. Death in children and adolescents was uncommon, with less than five deaths (<0.1%) observed in the 12 months following treatment with methoxyflurane and no deaths in those treated with both methoxyflurane and an opioid analgesic. Adverse drug reaction was rare (<0.1%) in patients treated with methoxyflurane, as was liver and kidney toxicity with no case observed. At 90-days follow-up, there was no significant difference in hospitalisation in patients treated with methoxyflurane and those treated with methoxyflurane and an opioid analgesic (aOR:1.01, 95% CI:0.85–1.21). Compared with methoxyflurane treated patients, patients treated with an opioid analgesic were more likely to be hospitalised (aOR:1.23, 95% CI:1.09–1.39).	III
	Inhaled	**Lam et al. 2025**[120] SLR of methoxyflurane studies (n=6 studies). All studies were considered of high to moderate quality. Baseline pain scores were comparable across all studies ranging from VAS 63–66 mm or an NRS of 4–7 with one study including patients with severe pain (NRS >8). Pain reduction was evident within 5 minutes of methoxyflurane initiation, pain reduction was up to VAS 30–39 mm and NRS (0–10 scale) −5.75, with pain reduction maintained up to 30 minutes post-initiation. However, comparator drugs like fentanyl and morphine were associated with a more durable analgesia over time. Compared with placebo, methoxyflurane-treated patients required fewer breaths of the inhaler to achieve pain relief and required less rescue analgesia. AEs were comparable between all treatment groups. Patient satisfaction with methoxyflurane was very good or excellent as measured on a 5-point Likert scale and ~95% reported high satisfaction compared with 64–68% of placebo-treated patients.	IA
	Inhaled	**Smyth et al. 2025**[121] PACKMaN was a double-blind, controlled, superiority randomised trial in the prehospital setting in ambulances. Patients aged >16 years were randomised to receive methoxyflurane and morphine (n=230 [51%]) or methoxyflurane and ketamine (219 [49%]). Primary endpoint was sum of pain intensity difference (SPID), which was comparable across all patients with no significant difference (SPID methoxyflurane plus morphine 3.4 versus 3.5 for methoxyflurane plus ketamine). Onset to pain relief was faster for ketamine treated patients whilst the duration of pain relief was longer for morphine treated patients. There was no difference in ED LOS or changes in vital signs. Both groups had comparable numbers of AEs but the most common AEs in the morphine group was hypotension and behavioural in the ketamine group.	IIB
NERVE BLOCK			
Bupivacaine, plus other anaesthetics not identified	Mixed nerve block, spinal block	**Abou-Setta et al. 2011**[122] A systematic review of pain management in hip fracture included 32 studies on nerve blockade and concluded that nerve blockades are effective for relieving acute pain and reducing delirium.	IV
Drugs not identified	Femoral nerve block	**Riddell et al. 2016**[123] A review of 7 studies of femoral nerve block in hip fracture reported decreased rescue analgesia requirements in 6 studies and no AEs.	IV

Therapy	Route of administration	Overview of study/data	Level of evidence
Bupivacaine	Femoral nerve block	**Morrison et al. 2016**[124] In an RCT including individuals with hip fracture in the ED, patients were randomised to receive femoral nerve block at admission followed by continuous fascia iliac block within 24 hours (n=79) or conventional analgesics (n=82). Pain scores 2 hours after presentation at the ED favoured the nerve block group over the control group (3.5 versus 5.3, p=0.002). At 6 weeks, participants who received nerve block reported better walking and stair climbing ability (mean Functional Independence Measure locomotion score of 10.3 versus 9.1, p=0.04).	III
Drugs not identified	Fascia iliac block	**Miller et al. 2016**[125] A national observational study in the UK received responses from 77% of all acute medical trusts in the UK. Of these, 62% of routinely provide fascia iliac compartment block for the management of pain caused by proximal femoral fracture.	III
Bupivacaine plus lidocaine	Brachial plexus block	**Galos et al. 2016**[126] Patients undergoing surgery for fixation of acute closed distal radius fractures were randomised to brachial plexus blockade (n=18) or general anaesthesia (n=18). Patients who received nerve block had lower pain scores at 2 hours after surgery (1.4 versus 6.7), but higher scores at 12 hours (6.0 versus 3.8) and 24 hours (5.3 versus 3.8).	III
Bupivacaine	Ultrasound guided fascia iliaca nerve block	**Kolodychuk et al. 2022**[127] A prospective cohort study in 65 patients in the ED with isolated femoral neck, intertrochanteric, and subtrochanteric femur fractures of whom 39 patients (60%) received nerve block with 40 ml 0.25% bupivacaine. In patients receiving nerve block opioid consumption preoperatively compared with those without nerve block (n=26), 17.4 vs 32.0 morphine milliequivalents, and a lower mean opioid consumption during their hospital each day (13.3 vs 24.0 morphine milliequivalents) and overall, during their hospital stay (54.5 vs 117.5 morphine milliequivalents). Patients treated with nerve block had a shorter length of post-ED hospital stay (4.3 vs 5.2 days). There was no significant difference in discharge disposition destination between groups and no patients reported complications.	III
Ketamine	Ultrasound guided peripheral nerve block	**Mohanty et al. 2023**[128] Prospective, open-label randomised study of 111 patients with isolated traumatic extremity injuries undergoing ultrasound-guided peripheral nerve block with ketamine. The primary endpoint was reduction in NRS by at least 3 points without rescue analgesia, and secondary outcomes were the need for rescue analgesia, adverse events and patient satisfaction. NRS was significantly lower in the nerve block group than IV ketamine dosing at all time points (30, 60, 120, 180 and 240 minutes post-dosing; p<0.001). More patients treated with nerve block reached the endpoint of NRS reduction ≥3 (100% vs 65% (−1.02 95% CI 1.42, 0.62). No patients in the nerve block group required rescue analgesia compared with 18% in the IV sub-dissociative ketamine dose group. NRS reduction from baseline was higher at 30 minutes for the nerve block group than IV ketamine group (treatment difference −2.17 [95% CI −2.64–1.69]). No patients experienced complications and patient satisfaction was higher in patients treated with nerve block than IV ketamine.	IC
Bupivacaine, ropivacaine	Ultrasound guided nerve block	**Bhattaram et al. 2024**[129] Retrospective analysis of ultrasound guided nerve block (femoral, fascia iliaca, serratus anterior) in 274 patients. Significant reductions in pain score post-block were observed with average NRS decrease of 2.9 ± 1.09 at 15 minutes and 5.8 ± 1.39 at 30 minutes. Complications were only recorded in 2 patients.	III

Therapy	Route of administration	Overview of study/data	Level of evidence
Bupivacaine	Peripheral nerve block	**Shinde et al. 2024**[130] Prospective, observational study in a single ED exploring the role of regional anaesthesia (variety of techniques including, adductor canal blocks (3.1%), fascia iliac blocks (12.6%), femoral blocks (7.4%), and axillary brachial plexus blocks (6.3%), among others. Mean VAS reduced from 8.8 to 1.9 ($p<0.001$) after bupivacaine administration, with 66.3% patients reporting pain relief within 5 minutes. Duration of pain relief varied: 41.1% had relief for ≤3 hours and 58.9% had relief lasting ≥3 hours. Most patients did not require rescue analgesia (89.5%). Adverse events were not reported, but authors indicate a place for peripheral nerve block in the ED but recognise the limitations of the study including its single centre design.	IIB
Ropivacaine plus dexamethasone	Ultrasound guided nerve block	**Pradhan et al. 2025**[131] Observational, descriptive, longitudinal study of peripheral nerve block for patients with upper limb fractures from distal humerus to distal phalynx. Primary objective was to evaluate onset and duration of ultrasound-guided peripheral nerve block with 0.2% ropivacaine plus 8 mg dexamethasone with 0.2% ropivacaine alone. Ropivacaine alone had a faster time to onset of pain relief (7.23 ± 0.83 minutes vs 10.31 ± 2.01 minutes) but duration of analgesia was significantly better for ropivacaine plus dexamethasone (duration 489.18 ± 78.34 minutes versus 591.29 ± 101.21 minutes; $p<0.0001$) as was reduction in pain score (mean VAS score 3.35 ± 0.12 vs 5.26 ± 0.23; $p<0.0001$). AEs were comparable in both groups, including hypotension, bradycardia and nausea with no significant difference between groups.	III
Bupivacaine OR ropivacaine	Ultrasound guided nerve block	**Abu-Halimah et al. 2025**[132] SLR of 9 randomised controlled trials of ultrasound guided nerve block for acute pain in the ED – no meta-analysis was possible. A range of nerve blocks were included although femoral nerve block for femoral neck and intertrochanteric fractures was most common. In all studies, pain reduction was effective with minimal side effects, but hypotension was observed in up to 8% of patients which was managed most typically with no intervention. Ultrasound guided nerve blocks were also linked to shorter ED stays, higher levels of patient satisfaction, and a low rate of complications when carried out by trained providers. It was concluded that included studies had low bias.	IC
Bupivacaine OR ropivacaine	Ultrasound guided nerve block	**Gawel et al. 2025**[133] SLR of SAPB in patients in the ED for a range of indications including rib fracture, tube thoracostomy, acute herpes zoster, chest wall burns, and unspecified chest wall injury either in the ED or in two cases to facilitate transportation to hospital. All blocks (n=82) were performed with bupivacaine or ropivacaine and in some adjuvants were also used including lidocaine, adrenaline, dexamethasone or methylprednisolone. Across all indications and studies pain reduction was noted with nerve block. Two studies in rib fracture showed pain reduction of up to NRS 3 or more. Similarly, in tube thoracotomy case studies indicated effective pain relief and patient preference for nerve block over procedural sedation. In many cases, onward requirement for opioids was reduced as was the need for other analgesics.	III

Therapy	Route of administration	Overview of study/data	Level of evidence
Bupivacaine plus dexamethasone	Ultrasound guided nerve block	**Goldsmith et al. 2025**[134] Prospective, multicentre, observational study in a convenience sample of sciatic nerve block in patients with acute sciatica to observe outcomes of ultrasound-guided transgluteal sciatic nerve block with bupivacaine (plus dexamethasone to improve duration of analgesia) with pain scores measured at 24 and 48 hours post-intervention. Sixty-three patients were enrolled and median pain scores reduced from 9 (IQR 8–10) pre-nerve block to 5 (IQR 3–7, p<0.001) at 24 hours and 4 (IQR 2–6.5, p<0.001) at 48 hours. Ambulation improved post-block with 27% unable to walk pre-block and reducing to 11% post-block. The ability of patients to 'get up and go' increased from 1.6% pre-block to 33% post-block (p=0.003).	III
Ropivacaine	Ultrasound-guided peripheral nerve block vs Bier block	**Tsao et al. 2025**[135] Open-label non-inferiority randomised controlled trial in adults aged ≥18 years with distal radius or ulnar fractures requiring reduction. Patients were randomised to ultrasound-guided supraclavicular block versus Bier block. Ultrasound-guided nerve block was non-inferior to Bier block (p<0.001). At 1-hour post-dosing pain was significantly lower in ultrasound-guided nerve block than Bier block (treatment difference -1.8 VAS). There were no differences in AEs between treatment groups. Ultrasound-guided nerve block was non-inferior to Bier block during closed reduction with prolonged analgesia.	III
LIDOCAINE			
	IA	**Cheok et al. 2011**[136] IA lidocaine (n=32) was compared with IV pethidine and diazepam (n=31) for the relief of pain during reduction of acute anterior shoulder dislocations. There was no significant difference between groups in terms of pain relief or patient satisfaction, and patients in the lidocaine group had a shorter duration of hospitalisation and fewer complications.	IB
	IA	**Wakai et al. 2011**[137] A Cochrane review of 5 studies (n=211) comparing IA lidocaine with IV analgesia with or without sedation for manual reduction of acute anterior shoulder dislocation in adults reported no significant difference between lidocaine and analgesia/sedation regarding pain during the procedure and post-reduction pain relief. Lidocaine may be associated with fewer adverse effects and a shorter recovery time.	IA
	IA	**Jiang et al. 2014**[138] A meta-analysis of 9 RCTs including 438 patients compared IA lidocaine with IV analgesia and sedation. IA lidocaine was not significantly different compared with IV analgesia and/or sedation for reduction of acute shoulder dislocation in the ED in terms of pain relief or patient satisfaction but did have a shorter duration of hospitalisation (p=0.03) and lower risk of complications (p<0.00001).	IA
	IV	**Soleimanpour et al. 2012**[139] Patients referred to the ED due to renal colic were randomised to IV lidocaine (n=120) or IV morphine (n=120). Patients in the lidocaine group had significantly greater pain relief than those in the morphine group at 30 minutes (p=0.0001).	III
	IV	**Firouzian et al. 2016**[140] Patients presenting to the ED with renal colic (n=110) were randomised to IV morphine plus IV lidocaine or IV morphine alone. Patients in the combination group had a reduced length of time to becoming pain free (87 versus 100 minutes) and nausea free (27 versus 58 minutes).	IIB

Therapy	Route of administration	Overview of study/data	Level of evidence
	IV	**Farahmand et al. 2018**[141] In a randomised study, patients with acute traumatic extremity pain were given either IV lidocaine (n=25) or IV morphine (n=25). Pain scores decreased significantly in both groups over 1 hour, with no significant differences between groups.	IIB
	IV	**Akhgar et al. 2021**[142] RCT of IV lidocaine versus IV morphine in 104 patients with mean pain score 8.23. Mean pain score was comparable in both groups except for 30 minutes post administration where IV lidocaine had a lower pain score 5.05 versus 6.39 (p=0.01).	IA
	IV	**Zhong et al. 2021**[143] Systematic review and meta-analysis of 12 randomised clinical trials in 1,351 patients with a range of pain conditions in the ED (abdominal pain, renal or biliary colic, traumatic pain, radicular low back pain, critical limb ischemia, migraine, tension-type headache, and pain of unknown origin) evaluated efficacy of IV lidocaine versus comparators (morphine n=6; ketorolac n=2; dexketoprofen n=2; hydromorphone n=1; fentanyl n=1). Pooled analysis indicated that IV lidocaine was as effective as comparator analgesia at all time points (15, 30, 45 and 60 minutes). No significant differences were observed in rescue analgesia requirements, but subgroup analysis indicated that rescue analgesia was required for patients in receipt of IV lidocaine with abdominal pain but not for MSK pain. Meta-analysis indicated no differences in the incidence of side effects between any study groups (OR: 1.09 95% CI: 0.59, 2.02 I^2= 48% p=0.78).	IC
	Patch	**Zink et al. 2011**[144] A retrospective analysis compared patients with rib fracture treated with lidocaine patch (n=29) with a matched control cohort (n=29). In the 24 hours after receiving lidocaine, patients in the active treatment group had a greater decrease in pain scores than controls (p=0.01). At 60 days, patients in the lidocaine group had a lower McGill Pain Questionnaire score, even though only 1 patient was still using a patch at this time point.	
	Patch	**Felemban et al. 2024**[145] Systematic review and meta-analysis of 10 randomised clinical trials in 523 patients indicated that lidocaine patches are more effective than placebo in controlling MSK and neuropathic pain in the ED, but efficacy data could not be pooled due to high levels of heterogeneity. Efficacy of lidocaine patches was comparable with NSAIDs in two studies, with no statistically significant difference in efficacy. The risk of adverse events was similar for lidocaine patches and comparators (risk ratio: 0.90; 95% CI: 0.48–1.67) but evidence was of moderate quality.	IC

(*) Study undertaken in patients with post-operative pain.
AEs, adverse events; aOR, adjusted odds ratio; AVPS, analogue visual pain score; CI, confidence interval; ED, emergency department; HR, heart rate; IA, intra-articular; IM, intramuscular; IN, intranasal; IQR, inter quartile range; IV, intravenous; LBP, low back pain; LOS, length of stay; MSK, musculoskeletal; NRS, numeric rating scale; NS, not significant; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; OM, oromucosal; PCA, patient controlled analgesia; RASS, Richmond Agitation Sedation Score; RCT, randomised controlled trial; SAEs, serious adverse events; SAPB, serratus anterior plane block; SBP, systolic blood pressure; SC, subcutaneous; SL, sublingual; SLR, systematic literature review; SoC, standard of care; VAS, visual analogue scale; VNPS, verbal numeric pain scale.

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CHAPTER 6:

Practical considerations for the assessment of pain in pre-hospital and emergency hospital settings

Overview of the practical implementation of pain assessment in emergency settings, emerging thinking and technology since 2020

Pain is a personal and entirely subjective experience and many patients presenting to the ED may not want analgesia (up to 35% of those with NRS ≥7 and 50% overall).[1] Pain is the most common reason for patients requesting ambulance attendance and presentation to the ED.[2,3] Effective pain management in emergency settings is critical not only for patient comfort but also to improve clinical outcomes and prevent pain-related complications (such as progression to chronic pain).[4]

Assessment of pain is a treatment imperative, and poor assessment of pain can lead to oligoanalgesia and worse patient outcomes, that can extend beyond the remit of the current acute pain incident. Understanding the patient's need for analgesia goes beyond the pain score alone. One study has indicated that a pain score of NRS 4.25 was a threshold for patients desiring analgesia.[1] Within the patient cohort of this study almost 20% of patients with a pain score NRS/VAS 0.5–3.0 expressed a desire for analgesia, whilst up to 35% of those with a pain score NRS/VAS 7–10 did not.[1] These data demonstrate that whilst the most frequent criterion used for analgesic provision is pain score, many patients in pain in the ED do not desire pain medications.[5]

Patients also interpret pain scores differently from professionals, which can lead to a miscommunication of analgesic need and potential under-dosing of analgesia if there is rigid following of guidelines based on numerical scores alone.[5] A further complication is the only moderate correlation between pain intensity and desire for analgesia.[6]

Given the practicalities of pain assessment in emergency settings and patients' needs and expectations, it seems prudent that the generally considered measure of analgesic success – 50% reduction in pain score – may not reflect the patient's experience.[5]

This chapter explores the practical implementation of pain assessment in the emergency setting. There is growing interest in pain assessment methods to go beyond those that might inadvertently encourage opioid use such as NRS and VAS and measuring pain intensity from the patient's perspective only.

It may be that composite tools that are observation-based as well as patient-report based may be more useful to provide an overall picture of the patient's experience of pain. Scores that include these perspectives include those such as PAINAD for dementia patients and PACSLAC for non-communicative patients (See **Chapter 3** for more details). Whilst no studies explore the role of pain score with desire for analgesia, one systematic review using secondary endpoints explores the multidimensional Defense and Veterans Pain Rating Scale (DVPRS) with the unidimensional NRS, with an emphasis on potential to reduce opioid use.[7] This review suggested that DVPRS might have the potential to reduce opioid use in patients who do not need it. Other studies in this review exploring patient satisfaction indicated improved

outcomes with the short forms of Brief Pain Inventory (BPI) and McGill Pain Questionnaire (MPQ) over both NRS and VAS.[7] Whether the implementation of such an approach may be appropriate for the emergency setting remains largely untested and should be explored.

For further information on a range of pain scales please see **Chapter 3**.

Pre-hospital

Acute pain remains poorly assessed in the pre-hospital setting,[8-14] with initial and final pain assessment absent in up to half of all cases.[10] More studies of pain assessment are needed as it is unclear if the true picture is that pain assessment is not carried out or is only poorly documented.

Recent data indicate that pre-hospital assessment remains poorly documented. In a Swedish abdominal pain study, pain was assessed in 55% of cases (n=447), median NRS=8 and 90% had moderate to severe pain.[15] In this study 62% received pharmacological analgesia and pain was assessed in only 50% of these.[15]

A study of hip fracture in the pre-hospital setting demonstrated that whilst most patients (>80%) received analgesia before reaching hospital leading to effective pain control (NRS reduced from 8 to 5), 80% of the overall patient cohort were not treated to agreed protocols with poor pain assessment was thought to be a major contributor.[16]

In practice, whether pain is assessed or not in the pre-hospital setting tends to be associated with the clinical condition and level of alertness of the patient, rather than the type of personnel present at the scene.[13]

Emergency department

Acute pain assessment remains suboptimal in the ED. Acute pain assessment should be considered a key priority for the ED, but it is poorly done and documented often because of other work priorities. Whether assessment is undertaken is largely reliant on the experience of the treating healthcare professional.[17]

A nurse study showed that whilst 96% of nurses believe pain management in the ED to be important or extremely important to the role of nursing in the ED, and they have an important role in nurse-initiated analgesia, more than half felt that pain was under-treated in the ED.[18] A second, similar study identified specific issues among nurses of evaluating pain in older patients, those with cognitive impairment or those mechanically ventilated. Little education is provided on the assessment of pain in these patients. Use of validated pain assessment instruments to assess pain in critically ill patients is poor.[19]

NRS, VNS and VRS scales are most frequently used but in one adult study >20% of ED nurses did not query pain leading to a high rate of patient dissatisfaction.[20] In children a correlation has been seen between higher pain scores and requests for analgesia when using the VRS and VAS scales, no such correlation was observed with the NRS.[21]

Assessment of pain should be undertaken as soon as possible, using medical history, physical examination and specific pain history (**Table 6.1**).[22]

Pain assessment in the ED should be mandatory at triage using validated scales, with documentation required for both initial and follow-up assessments. This ensures pain is recognised and addressed early in the patient journey.[17,23]

Barriers to effective pain assessment in emergency settings include patient volume and the workload involved in triage and patient care.[18] The implementation of protocols that mitigate such barriers should be considered wherever possible.

Table 6.1 Fundamental components of a pain history[22]

Site of pain	• Primary location of pain – description and diagram of pain location • Radiation of pain from primary location
Circumstances associated with pain onset	• Including details of trauma or surgical procedures
Character of pain	• Descriptors of sensation – sharp, burning, throbbing etc. • McGill Pain Questionnaire – sensory and affective descriptors • Characteristics of neuropathic pain using specific neurapathic pain questionnaires e.g. NPQ, DN4, LANSS, PainDETECT, ID pain
Intensity of pain	Intensity in different situations • At rest • On movement • Other temporal factors – Pain duration – Pain over time: current, last week, highest intensity – Characteristic of pain – continuous, intermittent
Associated symptoms	• Other symptoms e.g. nausea
Effect of pain on activities and sleep	• Interruptions to sleep, ability to undertake normal activities
Treatment	• Current and previous medications including dose, frequency, efficacy, side effects • Other treatment for pain • Which healthcare professionals have been consulted in relation to pain
Relevant medical history	• Prior or coexisting pain conditions and treatment outcomes • Prior or coexisting medical conditions
Factors affecting patients' symptomatic treatment	Understand non-medical factors including • Belief concerning the causes of pain • Understanding, knowledge, expectations and preference for pain management treatment • Expectations of outcome of pain treatment • The reduction in pain required for patient satisfaction • The patient's typical coping strategies for stress and pain (understand if patient has anxiety, depression or psychiatric disorders present) • Family/carer expectations and beliefs about pain, stress and management course

DN4, Douleur Neuropathique en 4 Questions; NPQ, Neuropathic Pain Questionnaire; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs

Tools for assessing pain in emergency settings

Self-reporting of pain should be used whenever appropriate, as pain is a personal and entirely subjective experience (see **Chapter 3**). A study in children indicated that adding caregiver reports to the FACES pain scale was not effective and was not recommended as a substitute for self-reporting.[24]

The choice of pain measurement tools must reflect the individual patient in terms of developmental, cognitive, emotional, language and cultural factors.[22] The inability to communicate verbally does not mean that an individual is not in pain and in need of analgesia, and a number of validated tools are available to assess patients in these circumstances.[25]

Multiple tools are available e.g. VRS, VAS, NRS none of which have been specifically validated in the ED and which may be limited by the unidimensional rating of pain reduction only and cannot reflect the emotional experience and unpredictability of pain.[5] Some studies indicate a mismatch between pain perceptions of physicians and patients (physicians lower than patients, p=0.004) which leads to under estimation and under-treatment,[26] with others suggesting a positive correlation between pain scores derived from physicians and patients.[27]

Unidimensional measures of pain intensity such as the VAS, NRS and verbal descriptor scales are more commonly used to quantify pain in the acute pain setting than multidimensional measures.[22] The NRS may be more practical than the VAS in a busy ED in that it is generally easier for patients to understand and also doesn't require patients to

have clear vision and manual dexterity, or for a pen and paper to be provided.[28] In one study, patients with mild-to-moderate pain preferred NRS, with other scales preferred by those with more severe pain.[29]

In adult patients who are alert, communicative and without cognitive impairment, the VAS and NRS provide a more sensitive measurement of pain than verbal descriptor scales.[28,30] Regular reassessment of pain is as important as the initial assessment, to monitor the effectiveness of pain management and the changing analgesic requirements of the patient.[31] Assessment should take place at a frequency guided by the patient's pain severity,[31] as well as the route of administration of analgesia and its time to onset of pain relief.

For the assessment of patients who fall outside of the alert, verbally communicative profile, the FLACC and FACES scales are recommended for use in young children and those with no and limited ability to communicate, respectively.[32-34]

The methods of assessing pain in elderly individuals should be driven by the presence and degree of cognitive impairment. While cognitively intact elderly individuals can be assessed in the same way as younger adults, a range of specialised tools are available for individuals with cognitive impairment and advanced dementia (see **Chapter 3**).[35-37]

There is a move towards assessment using multidimensional versus unidimensional pain scales with more accurate discrimination of pain,[5,7] but data remain limited. Multidimensional tools may be able to describe the complexity of pain sensation more accurately and have been hypothesised to be more useful in determining analgesic need. The impact of anxiety on pain perception is not fully understood, but it is know that anxiety in adults in the ED is a risk factor for oligoanalgesia and poor patient satisfaction.[38] An integrative review, suggested that construction of pain and anxiety tools into one easily implementable tool would provide a contextually appropriate guide to clinical assessment and management of pain.[38] Patient satisfaction was higher when multidimensional tools were considered.[7,39] The BPI-Short Form was completable within 4 minutes, which may be feasible within pre-hospital and ED settings, and provided outcomes relating to pain interference that correlated with NRS severity score.[39] It was preferred by patients and may be a more comprehensive and standardised tool than NRS.[39] Similarly, other multidimensional scales such as the DVPRS used in a civilian population may be able to differentiate between moderate and high levels of pain in ED settings.[40] In a study comparing DVPRS and NRS the ability of the DVPRS scale to discern moderate and high pain scores was considered potentially useful when determining whether opioids are appropriate.[40]

AI and machine learning are being implemented across healthcare but their use in emergency settings is largely for triage and prognostication in ED or pre-hospital settings or for emergency medical service dispatch.[41,42] AI has been used in postoperative settings to evaluate pain and is increasingly being used in chronic pain.[43] AI models that explore pain intensity are under exploration and show promise,[44] and a SLR of AI approaches to pain assessment not in the emergency setting suggests that AI approaches might improve pain recognition and pain scoring.[45] Given the pressures in the emergency setting both pre-hospital and in the ED there is potential to use AI as a tool to measure patient pain. Such a tool could incorporate multiple dimensions of patient understanding, physical parameters and facial expressions and may have use in patients unable to articulate their pain.

A recent consensus,[46] recommends mandatory training for all healthcare professionals to understand pain from the patients' perspective, and they should be supported to implement real time assessment. The use of AI tools for automatic pain assessment is recommended provided they are internally and externally validated and subject to appropriate update and any tool should be multidimensional, taking account of physiological signs, facial expression, speech, clinical data and patient self-reporting

Other assessments

Many patients with acute pain in the ED undergo other clinical assessments to provide additional information on the cause of their acute pain, which can in turn help to determine the optimal analgesic approach. Radiography, ultrasonography and CT are common in the management of acute abdominal pain, and provide a reasonable to good degree of sensitivity for the diagnosis of urgent conditions (88% for radiography, 70% for ultrasonography and 89% for CT).[47] Electrocardiograms, radionuclide myocardial perfusion, magnetic resonance imaging, CT and biomarker

analysis can all be useful to provide further information in patients with acute chest pain.[48] Ultrasound, sonography and CT are commonly used in female patients with acute pelvic pain in the ED.[49]

Improving pain management practices in the emergency setting

Clinical audit is a key quality improvement tool in both EDs and pre-hospital settings, systematically reviewing current care against explicit standards and enabling targeted interventions to enhance the assessment and management of acute pain. Clinical audit is important to ensure consistent, high-standard care and monitor adherence to pain management guidelines including pain scoring, documentation and ensuring equitable analgesia for all patient groups.[23,50] Audit of pain assessment and management in the ED and pre-hospital settings reveals common issues such as incomplete pain score documentation and under-treatment, prompting targeted education and policy changes that improve patient outcomes.

Audit is recommended at least annually by a range of bodies, including the Royal College of Emergency Medicine.[23]

Practical considerations for the assessment of pain: take-home messages

- **Pain is the primary reason why patients present to the ED and understanding how to recognise and manage pain is a clinical imperative.**
- **Pain is subjective and individual to each and every patient with components of emotional, physical and psychological determinants.**
- **Pain assessment is an essential tool in emergency settings.**
- **Training of emergency personnel regarding the importance and implementation of pain assessment is necessary to guide effective pain management.**
- **Assessment of pain should begin at triage and continue through to discharge – only with effective assessment can good pain management decisions be made. The initial assessment should include a general and a pain-specific medical history.**
- **All patients should be assessed for pain, and specific tools are available for those who are non-verbal, very young and cognitively impaired.**
- **Self-reporting of pain by the patient is the gold standard and whilst unidimensional tools of NRS and VRS are commonly used and may be useful in busy emergency settings, multidimensional tools should also be considered as these may be more discriminating between moderate and severe pain which may impact treatment options.**
- **Pain severity should be documented and pain management practices audited regularly, at least annually, to ensure equity and effectiveness.**
- **AI has an increasing role in healthcare provision and prognostication, and it may be that in the future AI will have a role in determining a multidimensional pain score that can be used to guide management.**

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CHAPTER 7:

Management of pain in pre-hospital and emergency hospital settings – considerations

Overview and consideration of the changing landscape in pain management, especially in the emergency setting since 2020

The last 5 years since the previous version of these guidelines were published have been shaped by the increasing opioid crisis that has stormed across the USA and Europe. This chapter explores management considerations to mitigate pain in both pre-hospital and EDs.

In the ED, severe pain is a common presenting complaint, and opioids have traditionally been the mainstay of treatment,[1] but it is essential that effective alternatives to opioids for the treatment of severe pain are explored including NSAIDs, paracetamol, and regional anaesthesia techniques.[2] Mitigating opioid use requires the implementation of a multimodal approach to pain management using combinations of non-opioid medications and non-pharmacological techniques to achieve pain relief.

Poorly managed acute pain in emergency settings (pre-hospital, ambulance, and EDs) has multisystemic physiological and psychological consequences, with emerging data from 2020–2025 highlighting risks ranging from cardiovascular stress to chronic mental health disorders.

Uncontrolled pain:

- **Triggers catecholamine release**, increasing heart rate (tachycardia) and blood pressure (hypertension), raising myocardial oxygen demand with potential to exacerbate underlying disease such as pre-existing coronary artery disease.[3]
- **Exacerbates respiratory complications** in up to 18% of patients with untreated pain in one study.[4]
- **Accelerates inflammatory cascade** elevating pro-inflammatory mediators, delaying wound healing and increasing infection risk.[4]
- **Induces hyperglycaemia** in up to 34% of people with diabetes with acute pain.[3]
- **Increases risk of central sensitisation** and future chronic pain, one study showed up to 12% of ED patients developed chronic pain at 3 months, an increase in the odds of chronic pain of 8.2.[5]
- **Alters somatosensory cortex connectivity** which has been linked to fibromyalgia-like syndromes.[4]
- **Impacts mental health** with uncontrolled acute pain in emergency settings leading to anxiety, pain catastrophising, and delirium in older adults.[4]
- **Places an economic and system burden** on pre-hospital and ED settings with increased risk of patient hospitalisation when pain is unresolved and increased healthcare utilisation post-discharge.[4,5]

Pain management principles

Management of pain starts before the consideration of pharmacological interventions and should consider patient expectations of pain management and non-pharmacological treatment interventions (See **Chapter 4**). The goals of analgesic therapy should be:

- **Setting realistic expectations:** functional pain control rather than elimination of pain.[6,7]
- **Patient buy-in and satisfaction:** shared decision-making when goals and limitations of analgesia are discussed transparently correlates with improved patient satisfaction.[8,9]
- **Functional outcome:** the ability to eat, sleep, ambulate, or participate in care often represents success, regardless of residual pain.[10]

Strategies for expectation management include:

- **Communication:** clearly explain pain management goals and anticipated results of interventions.
- **Pain assessment:** use validated pain scales (consider the use of multidimensional scales – see **Chapter 6**) and reassess after interventions to demonstrate progress.
- **Documentation:** record pain discussions and patient preferences as part of the care plan.
- **Empathy and reassurance:** listening to and validating a patient's concerns improves overall satisfaction, even in the absence of full pain resolution.

Pre-emptive analgesia should be considered in patients where escalating pain is anticipated and prompt implementation of analgesia once pain occurs is essential for patient comfort and satisfaction, prevention of transition of acute pain to chronic pain and psychological benefits for future pain.

First-line therapy for acute mild-to-moderate pain in the pre-hospital setting typically involves non-opioid analgesics. Paracetamol and NSAIDs are foundational treatments across Europe for conditions ranging from MSK injuries to abdominal pain. Guidelines in the last five years increasingly recommend maximising these agents before considering opioids, even for some severe pain scenarios.[11] While pharmacological analgesics are essential for the management of pain in the ED, the importance of non-pharmacological treatments should not be overlooked.[12]

The key challenges in the emergency environment – pre-hospital and the ED – are time constraints, variability in clinical protocols and the need to address a diverse range of patient needs, for example, children, the elderly and chronic pain patients and those presenting with analgesic overuse or opioid misuse.

Multimodal analgesia, combining pharmacologic and non-pharmacologic interventions acting at different sites within the pain pathway, has gained traction in emergency and pre-hospital settings since 2020, driven by efforts to reduce opioid reliance and improve pain management equity. The use of multimodal analgesia may help to optimise outcomes in the treatment of acute pain, reduce opioid-related side effects and prevent chronic pain.[13,14] A multimodal approach to analgesia should consider psychological interventions such as the sharing of information about the procedure and what the patient might expect to feel during it,[15,16] and distraction techniques such as the use of imagery, music and relaxation.[17-19] Importantly, implementation of a multimodal, multidisciplinary approach to analgesia has the potential to be opioid sparing but can also enable earlier implementation of analgesia during triage by nurses or pre-hospital personnel. A range of data exists that explores the role of nurse-initiated interventions in the ED setting, including nerve blocks, suggesting that analgesia implemented early by a range of personnel is feasible and effective.[20-24]

Whilst not in an emergency acute pain setting, a recent study has explored the impact of multimodal analgesia in perioperative pain management.[25] This study demonstrated improvements in target pain relief when an individualised, patient centric approach encompassing a plethora of approaches (medications, nerve blocks and non-pharmacological approaches) provided more effective, balanced pain control that was opioid sparing and improved patient outcome.

In busy, time-constrained emergency settings the implementation of a multimodal, multidisciplinary approach may seem daunting. It requires a holistic approach to overcome barriers and the creation of specific protocols for personnel to follow. An overview of barriers to a multimodal strategy for acute pain and possible solutions is provided in **Table 7.1**.

Table 7.1 Overview of challenges and mitigating approaches in implementing multimodal analgesia
Adapted from Nagpal et al. 2024[13]

Challenges	Issue	Possible solution	Outcome
Inadequate pain assessment	Use of current tools may capture only unidimensional parameters – pain may be under- or over-estimated and not account for the complete patient experience of pain	Develop and use more nuanced multidimensional pain assessment tools Improve communication with patients, including regular pain assessments Consider the use of AI algorithms and machine learning to predict pain	Personalised and enhanced understanding of individual pain and its impact
Opioid overuse	Risks of misuse or addiction, sometimes driven by cultural beliefs or perception of patients' socioeconomic status	Develop and implement opioid stewardship protocols that optimise pain relief through use of non-opioid analgesia in a multimodal approach	Reduced reliance on opioids without compromise on analgesia, potential for improved pain management satisfaction among patients
Lack of standardised protocols	Absence of uniform pain management protocols across emergency settings	Develop and agree standardised pain management protocols ideally aligned in pre-hospital and ED settings	Streamlined, consistent and timely implementation of pain assessment and analgesia, reduced variability of care, improved patient outcomes
Lack of patient report of pain	Vulnerable patients such as children, elderly may underreport pain due to communication difficulties or fear	Develop and implement improved communication tools along with regular pain assessment and healthcare professional training to recognise pain	Opportunity for improved effective analgesia
Emergency settings constraints – pressure and overcrowding	Workflow pressure can delay time to pain assessment and management intervention	Improve ED workflow, streamline pain assessment tools, triage pain severity and requirements, integrate multidisciplinary approach	Streamlined, consistent and timely implementation of pain assessment and analgesia, reduced variability of care, improved patient outcomes
Limited use of multimodal analgesia	Lack of awareness and training in implementation of multimodal approaches that include both pharmacological and non-pharmacological approaches	Enhanced education for healthcare professionals to encourage the use of multimodal approaches regarding pain management techniques that integrate both pharmacological and non-pharmacological modalities Develop multimodal protocols for emergency personnel	Reduce opioid use, optimise multimodal approach with potential for more effective comprehensive analgesia and can minimise side effects
Limited use of non-pharmacological options	Lack of awareness and training in implementation of non-pharmacological approaches and how they relate to different patient groups e.g. children, adolescents, adults	Integrate multidisciplinary pain teams into emergency settings to improve access to therapies, and education (both healthcare professional and patient)	Holistic pain management, with potential for reduced side effects and durable pain control
Patient expectations	Patients may expect immediate and absolute pain relief which may pressure HCPs to prescribe opioids	Communicate effectively with patients to understand expectations of analgesia and effective analgesia that may not include opioids Develop culturally sensitive pain management strategies and educational tools that are patient-friendly and easy to use	Patients have realistic expectations of pain, enabling effective use of multimodal analgesia

Role for opioids and opioid stewardship

Despite the emergence of the opioid crisis, they remain an important component of emergency pain management, especially for severe pain. Current practice in Europe is to use them judiciously and within structured stewardship frameworks. Morphine (IV) is traditionally considered the gold-standard for severe acute pain in the ED, indeed, many international guidelines have recommended IV morphine as the first-line treatment for severe pain (e.g. severe trauma, large burns).[26]

In the last five years, many European EDs have adopted opioid stewardship principles including protocols limiting opioid dose and duration, preference for short-acting formulations, and ensuring opioids are only prescribed when appropriate. EUSEM, in line with the Royal College of Emergency Medicine guidelines, advise that if opioids are needed, they should be the *lowest effective dose for the shortest duration* and generally not supplied beyond 2–3 days on discharge.[27] The use of long-acting opioids or fixed-dose combinations (like codeine/paracetamol) in the acute setting are discouraged due to the difficulty in titration and added risks.

Clinicians should also co-prescribe laxatives or antiemetics as needed and educate patients on tapering off opioids quickly when pain improves. Opioids should be considered as one component of analgesia (combined with non-opioids), rather than as a standalone solution.

Receipt of IV morphine has been correlated to clinician education and knowledge and the patient pathway.[26] In one study, patients with the most intense pain (NRS 10) received IV morphine (37.0%) compared with a NRS score <7 where IV morphine was significantly less likely to be used (p=0.01).[26] Organisational factors also determined IV morphine use, with those arriving in the ED by ambulance more likely to receive IV morphine (78.3%) and those attended by senior physicians more likely to be treated with IV morphine (63.0%) versus more junior physicians, suggesting a role for education. Patients discharged home compared with those admitted onward to hospital were less likely to receive IV morphine whilst in the ED.

Considerations for using opioids in acute pain management

When determining the use of opioids the following parameters should be considered.[10]

- Opioids should be used in the ED as a part of multimodal analgesia in conjunction with non-pharmacological and non-opioid therapies.
- Opioids should not be used as first-line analgesics in the ED or at discharge in patients with acute back pain, acute headache, acute MSK pain (except fractures), and acute dental pain as the associated risks of misuse, overdose, addiction are significantly higher than any pain relief provided.
- Morphine (IV, oral) in the ED and at discharge provides a better balance of adequate analgesia and reduced euphoria than other opioids and should be considered as the opioid of choice.
- In situations where morphine is contraindicated and opioid analgesia is still warranted; parenteral fentanyl is a suitable alternative in the ED and at discharge.
- Parenteral and oral hydromorphone should be avoided as a first-line opioid in the ED due to increased rates of respiratory and central nervous system depression (compared to morphine) as well as due to severe euphorigenic properties.
- Oxycodone should not be used in the ED or at discharge due to greater potential for euphoria, misuse, diversion, overdose, and the development of addiction with a lack of analgesic superiority to morphine and hydrocodone.
- Tramadol should not be used in the ED and at discharge due to its modest, at best, analgesic efficacy, high potential for misuse, and numerous adverse effects (e.g. hypoglycaemia, hyponatremia, seizures, serotonergic syndrome).
- Codeine plays no role in managing pain in the ED as it provides sub-optimal pain relief with significant genetic variability in analgesic response.
- If fast-acting opioids are required for patients in moderate-to-severe pain whilst other analgesic options are being established, consider the use of IN sufentanil, IN ketamine or methoxyflurane.

Pre-hospital pain management strategies

Best-practice acute pain management should be for patients to receive adequate treatment for their pain before reaching the ED. Management of pre-hospital analgesia often includes providing pain relief for procedures carried out at the scene of the emergency, most commonly limb realignments in the case of dislocations, extrication of trapped patients and splinting in the case of fracture, which often result in intense to severe pain and must be managed accordingly.[28] However, acute pain is often undertreated in the pre-hospital setting,[29-35] with many patients reporting moderate-to-severe pain receiving no analgesia at all.[31] This may be a result of patient refusal for IV administration due to needle phobia, and in these cases emergency personnel should consider detailed explanation so patients can make an informed choice. Pre-hospital pain management remains under recognised, underreported and undertreated with another studying showing 79.7% (n=177) of patients with pain receiving no pharmacological treatment, and in almost all treated cases pre-hospital personnel did not adhere to the treatment algorithm in use.[3] In this study, among those who were pharmacologically treated, pain statistically significantly decreased in intensity from before to after, in both emergency vehicles (nurse-staffed ambulances pre-medication 8.36±0.9 vs post medication 4.18±2.2, p<0.001; medical cars pre-medication 7.25±1.7 vs post-medication 3.50±2.6, p<0.001).[3] Subsequently, pain was only reassessed in 24.3% of subjects.[3]

Optimal pain management in the pre-hospital setting is subject to wide variations by geography and healthcare systems.[36] For example, in the UK opioids can be administered by paramedics pre-hospital but in Italy a substantial proportion of ambulances carry no analgesia.[29,33,34] Ketamine, nitrous oxide and methoxyflurane are commonly used in the pre-hospital setting and may provide useful alternatives to opioids.[36-42]

Studies of opioids in the pre-hospital setting are fewer than those for EDs and quality is often low but a systematic review suggests that IV opioids are comparable to one another and IN formulations are as effective and well tolerated as IV.[43]

Other data suggest:

- Fentanyl is the most commonly used opioid in pre-hospital settings; opioids are typically only used in patients with high pain scores but are associated with good improvements in pain score.[44]
- Opioids should be used with caution in elderly patients, one recent study suggested only 3% received pre-hospital opioids following a fall,[45] and are similarly used less often in children aged <10 years,[46] but opioids, of which fentanyl was most frequently used, was deemed effective and safe in children aged >10 years.[46]
- IN fentanyl is as effective a SC fentanyl except for adults aged >70 years where IN fentanyl may be more effective.[47]
- In a systematic review, IN sufentanil in pre-hospital and EDs was as effective as IV morphine with a safety profile comparable with morphine.[48]

Data regarding the use of nitrous oxide across studies is often of low quality, but a SLR in 2023 indicated that whilst nitrous oxide is superior to placebo it is less effective than morphine or inhaled methoxyflurane.[39] Nitrous oxide remains underused in emergency settings, particularly among children.[49]

Nitrous oxide use is not without issue, including contribution to Greenhouse Gases in the atmosphere being 298 times more able to trap atmospheric heat than CO_2, potential to deplete ozone, occupational exposure to both pre-hospital and ED personnel, and risk of abuse.[50,51] Recreational abuse of nitrous oxide has emerged over the last decade. Although data are largely limited to case reports and small case series and is a growing public health concern.[52] The impact of this in analgesic practice in pre-hospital and ED settings remains currently unknown.

Over the last 5 years since these guidelines were first developed, studies exploring the use of ketamine in the emergency setting have flourished. Ketamine is often combined with morphine in patients with acute trauma pain, and can reduce morphine requirements in these individuals.[36] Ketamine is particularly useful in a pre-hospital setting as, in addition to its opioid-sparing effect, it provides effective analgesia without respiratory depression and has little effect on blood pressure and pulse rate.[53]

In the pre-hospital or ED setting the use of IN or nebulised formulations may be most relevant, when IV availability is non-existent or limited or IV patient access is not possible. Nebulised ketamine in a case series has demonstrated effective pain control in adults and children that was comparable to IV ketamine and a low dose of 0.75 mg/kg was found to be effective.[54-58] IV ketamine was comparable to IV morphine and low doses may be equally effective to morphine in short-term use (<120 minutes).[59,60] US evidence-based guidelines for the pre-hospital setting[61] recommend the use of IN fentanyl over IV opioids where IV access is difficult, given its efficacy, ease of use and acceptance by patients and providers.

Inhaled methoxyflurane has a place in the pre-hospital setting, as it is easy to prepare and use for both health personnel and patients, with a fast onset. It is suggested in a SLR that methoxyflurane can provide comparable pain reduction to paracetamol, NSAIDs like ketoprofen, and opioids like fentanyl or tramadol and is superior to nitrous oxide.[39] Two further SLR and meta-analysis of methoxyflurane, specifically in emergency settings, demonstrated fast onset of analgesia within 5 minutes that is maintained over time and efficacy is comparable with standard analgesics.[62,63] Similarly, it has demonstrated superior efficacy to IM tramadol with a faster onset to effect and higher paramedic and patient satisfaction.[64] A Swedish ambulance study indicates that methoxyflurane provides effective pain control by the time of ED admission, using an average of two inhalers, with pain relief typically achieved within 17 breaths.[65]

IV NSAIDs are recommended over IV paracetamol.[61] If the oral route is available then paracetamol or NSAIDS should be considered. A study by the UK Ambulance Service,[66] demonstrated comparable efficacy of paracetamol (both oral and IV) when used alone. A study comparing the use of IV paracetamol plus IV opioids versus IV opioids alone (ADAMOPA study) is underway to explore efficacy.[67]

Other studies of IV paracetamol plus IV opioids, such as hydromorphone, in the emergency setting have shown increased efficacy when used in combination,[68] but does not appear to be opioid sparing.[69]

It has been suggested that NSAIDs should be avoided in cases of fracture, however more recent data indicate that the early use of NSAIDs appears to reduce post-trauma pain, reduces the need for opioids and has no impact on fracture healing.[70,71]

Despite recommendations, analgesic provision across Europe will be dependent on analgesic availability and the training of emergency personnel.

Emergency department pain management strategies

Following assessment of a patient's pain, the appropriate analgesic in the ED must be selected, considering its benefits and risks with reference to the individual patient and considering both pharmacological and non-pharmacological approaches. Once analgesia has been provided, patients must be reassessed to ensure that their pain is being successfully managed, and their pain relief regimen should be re-evaluated regularly during their stay in the ED.[72] Any barriers to pain management should be discussed with the patient and family member to identify potential solutions.[72]

In the ED, a wider range of analgesic options are available to clinicians as well as the potential to administer medications in modes that may be more acceptable to patients. Capitalising on the CERTA approach to multimodal analgesia, healthcare professionals should consider combination analgesic drugs that operate through different mechanisms of action.[73] This approach provides opportunities to combine strong analgesics with simple analgesics such as opioids with NSAIDs to optimise pain control because of their different mechanisms of action. A study in 600 patients suggests optimisation of treatment is more important than the analgesics chosen, with no clinically meaningful differences observed between 5 oral analgesics including paracetamol, ibuprofen, hydrocodone/paracetamol, oxycodone/paracetamol and codeine.[68]

Paracetamol

As in the pre-hospital setting,[66] IV paracetamol was effective in managing pain in the ED but when used in combination with opioids did not demonstrate capability to be opioids sparing,[74] these results are broadly reflected in other studies where IV morphine was compared with combined IV morphine and IV paracetamol with no efficacy benefits observed

and no difference in opioid consumption.[69]

In older patients, IV paracetamol was shown to be as effective as IV hydromorphone 1 hour after administration with a comparable need for rescue medication in both treatment groups.[75] More adverse events were reported by those receiving hydromorphone, but differences were not clinically meaningful. Importantly, regardless of treatment many patients remained in pain.

NSAIDs

With NSAIDs there are data suggesting that low and high doses provide equivalent analgesia but there may be an increased need for rescue analgesia when low doses of NSAIDs are used,[76,77] and the choice of NSAID may be relevant for example, ketorolac more effective than ibuprofen especially in children but data are limited.[78] Studies suggest there is limited difference between NSAIDs and paracetamol with comparable efficacy and no benefit to combination or sequencing,[79,80] whilst another study indicated no efficacy difference between IV paracetamol, ibuprofen or dexketoprofen.[81] However, patients treated with IV NSAIDs are less likely to require rescue analgesia than with IV paracetamol whilst providing comparable analgesia to both IV paracetamol and IV opioids.[82] Proton pumps should be considered in patients where NSAIDs are to be used long-term (mostly typically in those with inflammatory conditions like rheumatoid arthritis). For those with acute pain in emergency situations it may be wise to consider proton pump inhibitors in those at moderate risk of gastrointestinal ulcer including age >65 years, when high doses of NSAIDs are being considered, in those with a previous history of peptic ulcers or concurrent use of low dose aspirin, corticosteroids or anticoagulants.[83]

Opioids

Although opioids are commonly used in this setting, several considerations should be considered when deciding whether to administer opioids to a patient with acute pain. These include the high associated administrative burden, including the requirement for patient monitoring after receiving an opioid (from ≥1 hour to an overnight stay, dependent on local protocols); the burden of managing analgesia given via the IV route; special regulations, staff training and certification requirements, and storage and prescribing procedures associated with controlled substances.[37]

Opioids are also associated with a higher incidence of adverse reactions than some other analgesic options, particularly in opioid-naive patients.[84] Notable side effects of opioids include nausea and vomiting, sedation and respiratory depression, itching and allergic reaction.[84-86] The route of opioid administration should also be considered with data indicating that PCA provides comparable efficacy to IV opioids but is preferred by patients,[87] and may have benefits in terms of overall opioid consumption and decreased pain score.[88] Similarly, several studies and systematic reviews[48,89,90] have demonstrated that IN sufentanil has potential in the emergency setting with a fast onset of action that is comparable in efficacy to standard of care analgesia and IV opioids (such as morphine) with similar results observed with IN fentanyl.[47,91,92]

Ketamine

As in the pre-hospital setting the use of ketamine has gained traction, with data indicating efficacy with bolus plus infusion regimens (0.15 mg/kg bolus plus 0.15 mg/kg infusion over 30 minutes),[93] low doses (0.15 mg/kg over 15 minutes or 30 mg/kg single dose or doses <0.3 mg/kg),[54,60,94] and comparability of analgesic efficacy with opioids whether delivered by IV or by IN.[38,59,95,96] A SLR of 15 RCTs demonstrated efficacy of ketamine compared with IV morphine with lower incidence of adverse events, but analgesia is best in the early period post-dosing and may be less durable than morphine.[97] As in pre-hospital settings, nebulised ketamine is suggested to have a role in the ED, with meta-analyses indicating comparable efficacy to IV morphine.[98] A SLR of IN ketamine[99] demonstrated that IN ketamine was comparable with IV analgesia with no differences reported in use of rescue medication so has the potential to limit reliance on opioids, findings that are replicated in other meta-analyses[95] with studies[100] suggesting a role for ketamine in emergency settings. IN ketamine in older adults is as effective as IV morphine in short-term analgesia with limited need for rescue treatment.[101] Nebulised and IN ketamine provide an opportunity to deliver analgesia that is effective and may be more acceptable to patients, particularly for specific patients such as children[56-58,95] and in one dose comparison study low dose nebulised ketamine of 0.75 mg/kg was as effective as

higher doses.[55] As with other formulations, oral ketamine is an effective analgesic but efficacy is not enhanced by the addition of paracetamol.[102]

A SLR compared ketamine across formulations in children as an opioid alternative and indicated that ketamine was as effective as IV morphine and IV tramadol, but was associated with a higher rate of temporary adverse events.[103] Ketamine may have the potential to be opioid sparing, as shown by its comparable efficacy to opioids[59,104] at least up to 2 hours post-dosing[60] after which supplementary analgesia may be required.[105]

Methoxyflurane

The use of inhaled therapies like methoxyflurane is increasing within the ED. In the previous 2020 guideline, methoxyflurane was emerging in Europe. Now, 5 years later there is considerable evidence to support its use in pre-hospital and ED settings.[62-64,106-108] Two systematic literature reviews and meta-analyses[62,63] demonstrated a significant analgesic effect compared with standard of care analgesic ($p<0.0001$), with a fast onset to analgesia reducing pain to ≤30 mm on VAS or 5 on NRS and a high degree of patient satisfaction. The MEDITA study analyses have demonstrated a faster onset of pain relief compared with standard analgesia (9 minutes compared with 15 minutes)[108] and is as effective in elderly patients as in younger patients.[107] Methoxyflurane has also demonstrated superior efficacy compared with IM tramadol[64] whilst the InMEDIATE study suggests that inhaled methoxyflurane has the potential to reduce ED stay.[109] In severe pain, methoxyflurane has demonstrated clinical efficacy in the PENASAP study as part of a multimodal analgesic strategy including opioids.[110]

IV anaesthetics

IV anaesthetics such as lidocaine might be a good choice over IV morphine or IV tramadol with demonstrated efficacy and a fast onset to effect.[111,112] Lidocaine can also be administered in a patch which may be highly acceptable to patients and has demonstrated good analgesic efficacy.[113]

Nerve blocks

The ED provides opportunities for other approaches to pain management including nerve blocks,[114,115] which can provide effective analgesia, with a recognised good tolerability profile, reduced risk of delirium and shortened ED stay.[116] Use of ultrasound guided nerve blocks have demonstrated efficacy in a range of recent studies to improve pain and patient function,[117,118] and may be more effective than other methods of nerve block, for example, ultrasound guided supraclavicular block for upper-limb fracture compared with Bier block[119] or low doses of ketamine.[120] In studies nerve blocks are shown to be effective with a fast onset to effect,[114,115] and depending on the anaesthetic use, potential for durable analgesia.[115] With nerve blocks in the ED, patients report subjective and objective improvements in pain with few or no complications reported,[121,122] and provides the opportunity to be opioid sparing.[122]

However, for nerve blocks to be of use in the ED there is a need to integrate advanced pain relief techniques into emergency medicine training programs, contributing to a comprehensive approach to acute pain management,[117] including development and implementation of effective protocols and training,[123] driving buy-in from ED leaders and hospital stakeholders.[116]

Others

Other medications such as topical capsaicin have demonstrated efficacy against topical NSAIDs in the ED,[124] but data are limited and it is unclear how widespread the availability of capsaicin might be across Europe. Similarly, medications such as methocarbamol are suggested as efficacious in acute pain – comparable to diazepam and opioids – and may be opioid sparing but data are limited and the availability of drugs like this in emergency settings is unclear.[125,126]

Non-pharmacological approaches to acute pain management in emergency settings

While pharmacological analgesics are essential for the management of pain in the ED, the importance of non-pharmacological treatments should not be overlooked.[12] These include:

- Psychological interventions such as the sharing of information about the procedure and what the patient might expect to feel during it.[15,16]
- Establishing patient trust, especially in children, has been shown to be effective in gaining their cooperation and enabling implementation of analgesia.[127,128]
- Distraction techniques such as the use of imagery, music and relaxation, may be most appropriate to acute pain in the ED,[17-19] although robust clinical evidence specific to this setting is currently lacking.

Virtual reality (VR) has emerged as a promising non-pharmacological intervention for acute pain management in EDs and pre-hospital settings. A review by Viderman and colleagues evaluated all current evidence and demonstrates that VR can be successfully employed to control pain, including acute, perioperative, periprocedural and chronic.[129] A Swiss emergency department study demonstrated significant pain reduction (median NRS 4.5 to 3.0, $p<0.001$) and anxiety reduction (median NRS 4.0 to 2.0, $p<0.001$) following 20 minute VR sessions in 52 adult patients with traumatic and non-traumatic pain. Systematic reviews confirm VR's effectiveness across medical procedures, with 83% of studies reporting decreased pain intensity compared to controls.[130,131] The underlying mechanism involves immersive distraction, where VR redirects limited attentional capacity away from pain processing. Meta-analyses of 92 randomised controlled trials (n=7,133) showed significant pain score reductions (standardised mean difference −0.78, 95% CI −1.00 to −0.57) across diverse procedures including venipuncture, wound care, and procedural pain. VR demonstrates effectiveness in emergency department settings specifically, with studies showing comparable analgesic effects to moderate opioid doses.[132-134]

Modern standalone VR headsets (e.g. Oculus Quest 2) overcome previous implementation barriers, making emergency and prehospital deployment feasible. High user satisfaction, good tolerability, and minimal side effects support VR's integration into multimodal acute pain protocols. While prehospital-specific evidence remains limited, the technology's portability and immediate availability suggest promising applications for ambulance services managing acute trauma and medical emergencies.[130,133,135]

Pain management in special populations

Despite advances in pain management, the elderly, cognitively impaired or those with communication issues, children and ethnic minorities remain less likely to receive effective analgesia than other patient groups.[136,137] Research highlights systemic biases, communication barriers, and protocol gaps that exacerbate risks for groups such as these. These disparities often lead to prolonged suffering, increased complications, and long-term health consequences.

Children

Understanding the issues and biases that exist when confronted with the child in pain in emergency settings is important to optimise care.

There are disparities in the delivery of analgesia to children. In a US study, overall median time to pre-hospital analgesia in children was 39 minutes but this was up to 55 minutes for Hispanic children, compared with Black, White or other minority children (38 minutes, 37 minutes and 32 minutes, respectively).[138] Another study in the USA also indicated that Black children, like Hispanic children were less likely to receive opioid analgesia for limb fractures or suspected appendicitis.[139] An Australian study of methoxyflurane and opioids in children in pain in the pre-hospital setting showed that Aboriginal children and those from lower socioeconomic groups or living outside of cities were less likely to receive any analgesia.[40]

When their pain is assessed young children may struggle to self-report pain leading to reliance on observational tools,[140] whilst adolescents often underreport pain due to social stigma.[139,140] A study in children noted differences in

pain assessment and analgesic management in those with trauma pain and non-trauma pain.[141] Teenagers with trauma pain patients were more likely to be assessed and receive analgesics, however compared with younger children (aged <5 years) teenagers overall were less likely to receive analgesia.[141]

In children, the use of IN and inhaled medications such as IN fentanyl and inhaled methoxyflurane may be useful as single drugs or in combination with other analgesics.[42] These medications are well tolerated, easy and fast to administer with rapid onset and short duration of action and would seem to be drugs of choice, but both require patient cooperation and may not be suitable for those with facial trauma.[42] A retrospective cohort study in children aged <18 years demonstrated that those treated with methoxyflurane were typically younger than those provided with opioids, and less likely to be hospitalised.[40] However, methoxyflurane was as effective as opioids in controlling pain in children.[40]

It is recommend that pharmacological management of pain in children contains both non-opioid and opioid agents as well as non-pharmacological methods as appropriate (see **Chapter 8**). Trust forms the bedrock of the doctor-patient relationship. While establishing trust is a foundational skill for healthcare providers who care for children, there is no systematic approach to teaching this skill set, nor is there formal training during medical school or beyond. Krauss and colleagues have defined the elements required to establish trust and describe a methodology for achieving this.[128]

Older adults and elderly patients

Studies have indicated that detecting, assessing and managing pain in elderly patients with cognitive impairment is challenging[142] and requires a broader approach to include appropriate observation tools and involvement of family/carers.

Barriers to accessing and receiving effective analgesia in older adults include:

- Cognitive impairment
- Hearing and/or visual impairment
- Patients less likely to ask for help.

Providing effective analgesia to older patients is a common challenge faced by emergency physicians. Older patients have been shown to be at greater risk of oligoanalgesia,[31,143] and in the ED are up to 20% less likely to receive treatment than younger patients.[144] Data regarding oligoanalgesia in elderly patients is mostly old, predates the scope of this updated guideline (2020–2025).[145,146] However, three studies indicate that older trauma patients aged >65 years in a pre-hospital setting remain less likely to receive analgesia.[147,148,149]

Similarly, those with cognitive impairment who are often, but not always, older adults are also most likely to wait longer to receive analgesia and less likely to receive analgesia[136,150] reflecting the need for prompt and nuanced pain assessment in emergency settings, as outlined in **Chapter 6**. Among the elderly, analgesics in the ED were more commonly used in women, most typically an NSAID, with analgesic use increasing with age, and increasing use of paracetamol plus metamizole use with decreasing NSAID use, and consistent opiate use regardless of age or sex.[151]

Analgesia should be selected based on patient-specific risks (e.g. polymorbidities, chronic abuse of analgesics, impaired renal or hepatic function) and preferences, alongside frequent reassessment and treatment titration as needed. Whilst there is a need for consideration of age and polypharmacy when considering analgesia for elderly patients, for many treatment options efficacy and safety of analgesics are comparable in younger and older patients.

Patients with kidney disease

Pain is highly prevalent in patients with chronic kidney disease (CKD) and those presenting with renal complications, and poorly managed pain in this group is linked to decreased quality of life and survival.[152,153] Assessment must consider the cause, severity, and type of pain, as well as the patient's level of kidney function and concurrent comorbidities.[2,152]

For all patients, particularly those with reduced drug clearance, a multimodal, stepwise approach to analgesia must be adopted. First line approaches should emphasise non-pharmacological and non-opioid interventions wherever possible.[2,153,154] Analgesic selection and dosing must account for reduced renal clearance, comorbidities, and potential drug interactions.

In patients with kidney disease, paracetamol is preferred for mild-to-moderate pain as it has demonstrated minimal nephrotoxicity.[152,154] However, dose adjustment is recommended in advanced kidney disease. NSAIDs may be used with caution for the short-term but they may exacerbate kidney injury particularly with chronic use or in those with severe CKD.[152,154] Close monitoring is essential.

In patients with kidney disease, opioids should only be used when pain cannot be controlled by any other means. When opioids are used, healthcare professionals should consider using those with a lower renal clearance than fentanyl, methadone and hydromorphone.[153,154] Morphine and codeine should be avoided in these patients due to active metabolite accumulation, increasing the risk of neurotoxicity and respiratory depression.[152,153]

Whilst specific data in patients with kidney disease are lacking, IN ketamine has good efficacy with a fast onset to effect but methoxyflurane should be used with caution in patients with renal disease.[155]

Patients with liver disease

Acute pain is common in patients with liver disease – affecting up to 80% of people with liver disease – but management is complicated by impaired liver function, altered pharmacokinetics, comorbidities (such as coagulation disorders and encephalopathy), and elevated risk of drug toxicity.[156-159] Pain aetiology, severity, liver disease stage, and risk of hepatic encephalopathy must guide analgesic selection and dosing.[156,158]

Non-pharmacological interventions and a multimodal analgesic strategy should be prioritised to reduce reliance on medications with hepatic metabolism.[156] A tailored patient-centric approach is essential and a multidisciplinary approach including hepatology and pain specialists should be considered.[156] One of the greatest limitations of medication selection in those with liver disease is the reduction in hepatic clearance of certain medications, which most often leads to increased drug exposure.

Medication-related toxicities are already elevated in patients with liver disease so managing their pain is challenging. NSAIDs should be avoided in those with severe liver disease and used with caution in those with mild-to-moderate liver disease. Paracetamol should be use at a total daily dose ≤2 g in divided doses and can be used at these doses even in patients with severe liver disease.[160] Metabolism of morphine, hydromorphone and oxymorphone may give them a theoretical lower risk of issues in advanced liver disease.[160] Fentanyl and buprenorphine may also be preferred due their relatively safer hepatic profile, but all opioids require dose and dosing frequency reductions.[156,157,160]

Pregnancy

Analgesic prescribing during pregnancy is challenging, with the general rule being to avoid any medication, and whilst many analgesics may be considered safe to use there are specific considerations to be noted.[161] Non-pharmacological treatment should always be considered before analgesic medications are used. Paracetamol is regarded as safe in all three trimesters and is the analgesic of choice for pregnant patients with no risks noted for congenital abnormalities or spontaneous abortion.[162] NSAIDs, in particular ibuprofen, are best avoided but can be used in the second trimester[162] but should be avoided in the third trimester because of the risk of premature closure of the ductus arteriosis.[163] Evidence for opioids in pregnancy is largely limited to pregnant patients abusing opioids, which is associated with adverse neonatal outcomes. Short-term use of opioids for pain in pregnancy does not, however, appear to be problematic for patients or foetuses.[27,161] The opiates best to use are morphine and codeine, but they should be avoided during delivery.[27,161] Although nitrous oxide is not absolutely contraindicated in pregnancy it should be used with caution as it can have maternal and foetal side effects, most data confine the use of nitrous oxide to labour pain rather than emergency pain or for termination of pregnancy.[164-166]

Ethnic minorities

As noted previously, patients from ethnic minorities may be underserved with respect to effective pain control in pre-hospital settings[138] and are less likely to receive opioids or ketamine.[167] Across the spectrum of analgesia prescriptions people of an ethnic minority were significantly less likely to receive opioid analgesia.[168-170] Another study in children also noted that non-white paediatric patients were less likely to receive opioids.[137] There was no difference by sex for any analgesia but time for females to receive analgesia was longer.[137] All of these studies are from the US where the opioid crisis has accelerated in a different way to Europe. European data are lacking, and further research would be welcomed.

Patients with sickle cell disease and sickle cell crisis

Acute pain crises (vasoocclusive episodes, VOC) are the most common reason for emergency visits in sickle cell disease (SCD). Patients should be prioritised for fast triage and assessment to rule out complications and assess pain severity, as delays lead to poorer outcomes.[171-173] There are no objective measures for pain severity in SCD, so management relies on the patient's report of pain and previous effective regimens – their report of pain should be considered gold standard.[174]

Whenever possible, use individualised pain protocols based on what has previously worked for the patient as these have potential to improve pain scores, length of stay in the ED and time to first opioid analgesia.[175]

Opioids have long been considered standard therapy for VOC in SCD and should be administered promptly within 30–60 minutes of arrival to the emergency setting. Both the National Heart, Lung, and Blood Institute (NHLBI) and American Society of Hematology (ASH) guidelines from the USA recommend weight-based or individualised opioid protocols, followed by reassessment every 15–30 minutes until pain is managed.[176,177] One study has demonstrated that implementation of individualised opioid dosing in SCD over a weight-based regimen provides superior pain relief in terms of time to analgesia and also extent of analgesia and this approach should be considered.[178] In patients presenting with VOC there is an opportunity to consider immediate use of IN or OM opioids such as a fentanyl lolly to manage pain whilst considering longer term plans.

NSAIDs are widely used for SCD but to date studies have shown no significant reduction in the duration of VOC or pain score nor any opioid-sparing capacity.[174]

Ketamine has demonstrated good efficacy in emergency settings and has flexibility in administration (IN, nebulised, IV and oral). Low doses of IV ketamine have been used and reported in case studies of VOC and acute and chronic SCD pain,[179] especially when pain is refractory to opioids[180] although the supporting evidence remains of low certainty.[14] Data supporting the use of IN or nebulised ketamine in VOC treatment in SCD is currently lacking, but this route of administration may be useful for these patients.

It must be noted than many patients with SCD will have a hospital plan that should be consulted by healthcare professionals and implemented. Further, escalation of pain management should be considered specifically for this population and not escalated in line with other chronic disease, failure to do so can lead to population bias as has been seen with ethnic minorities.

Patients receiving opioids for chronic pain

Any patient in receipt of analgesia for chronic pain conditions presenting with new acute pain needs to be assessed on a case-by-case basis to ascertain the cause. Data supporting the use of opioids in the ED for treatment of acute exacerbation of chronic, non-cancer pain demonstrates higher likelihood of harm rather than benefit.[10] In patients currently receiving opioids, the amount of opioid used daily prior to the onset of the new pain must be determined and adequate doses of opioid need to be prescribed to treat baseline pain in combination with short-acting opioids to address the new acute pain.[27,181] Opioid analgesics should not be routinely used in the ED for chronic non-cancer pain with a notable exception of vasoocclusive crisis of SCD.[10]

Acute pain management in patients with opioid misuse disorder

Managing acute pain in patients with opioid use disorder (OUD) or those receiving opioid substitution therapy (OST)—such as methadone, buprenorphine, or naltrexone—poses significant clinical challenges, leaving patients often undertreated.[182] These stem from pharmacological complexities, altered pain physiology, and concerns around relapse, withdrawal, and under-treatment of pain. Evidence of interventions for patients with OUD are limited. However a recent systematic review suggests the use of oral clonidine, IM haloperidol and midazolam with IV morphine or IV lidocaine may improve pain outcomes.[183]

Methadone is not analgesic at maintenance doses and additional analgesia will be required in these patients, without disruption to their dose of methadone or buprenorphine wherever possible to minimise the risk of withdrawal or risk of relapse. In those on buprenorphine, as a partial antagonist of opioid receptors it will provide some analgesia and this should be considered when determining dosing of other opioids.[184]

Management of patients with OUD goes beyond therapeutic management and requires healthcare professional education of opioid-induced hyperalgesia, opioid tolerance and implications for management in those receiving opioid substitution therapy.[185,186] Patients need assurance that their pain will be assessed and managed appropriately as patients may be anxious about stigmatisation and denial of analgesia. Inadequate treatment of pain in patients on opioid replacement therapy (e.g. methadone or buprenorphine/naloxone) commonly leads to disruptive behaviour by angry and frightened patients who then may discharge themselves against medical advice, often to the detriment of the their health. Opioid induced hyperalgesia complicates the pain response reducing sensitivity to pain and opioid tolerance poses a problem when considering doses of opioids to use for the presenting acute pain.

Drug-seeking behaviour

There will be occasions when patients presenting with a chief complaint of pain may raise suspicions of drug seeking behaviour, an issue that is likely to increase as concerns regarding opioid prescribing emerge in Europe. A careful history and patient review are required to balance the risk of supplying drugs inappropriately with denying effective analgesia to patients with genuine pain. Until more information is available, unless there is strong evidence to the contrary, an assumption must be made that the patient is in real pain and appropriate analgesia supplied,[27,187] given that a primary role for clinicians is the alleviation of patients' pain. However, is it prudent to consider how quality improvement programmes might be instituted in the ED to provide integrated case management by specialist teams across the system for these vulnerable individuals.[188]

In patients addicted to opioids who are reporting genuine pain, consider the use of non-opioid approaches such as steroid injections, radiofrequency neurotomy, nerve blocks or non-pharmacological approaches.[189]

Drug seeking individuals may display characteristics including, but not limited to:[190]

- Inconsistent behaviour from the triage/waiting room to the treatment area
- Appearing to be in less pain when think not being observed
- Presenting with specific, often subjective complaints e.g. back pain, headache
- Excessively talkative, friendly or helpful
- Suggesting specific medications or dosages
- Claims of extraordinarily rapid relief from injectable medications
- Claiming allergies to non-narcotic medications.

Pain management in neurodivergent people

Pain perception is a complex process and individuals with neurodivergence including those with autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and Tourette syndrome can experience increased pain sensitivity and may exhibit an atypical response to pain although data on this phenomena are limited.[191-193] Further, people with neurodivergent conditions such as ASD may struggle to communicate their pain and need for analgesia.[194]

To optimise assessment and management of pain in people with ASD clinicians might consider:

- Environmental modifications
- Adjustments of language to the patient
- Time and patience with patients
- Inviting input from others
- Using measures and assessment scales appropriate for use in ASD such as Quantitative Sensory Testing.[191]

All of these modifications and an understanding of neurodivergence and its impact on pain perception and presentation require education of parents, caregivers and also healthcare professional staff.

Logistical considerations

Patient-controlled delivery of analgesia should be considered where appropriate and possible, since it provides a rapid response to patients' changing requirements for pain relief and removes some of the burden of management from hospital staff.[195]

Evidence suggests that PCA also results in greater patient satisfaction than physician-managed analgesia,[196-198] and reducing delays in analgesic administration may lead to patients leaving the ED faster.[199]

In a post-hoc analysis of real-time data, timely delivery of analgesia after arrival, rather than the adequacy of the pain relief, was shown to be associated with a shorter ED stay.[199] The chances of patients receiving adequate, timely analgesia are related to time and resources within the ED.[200-202] A greater delay in a patient receiving their first analgesia has been significantly correlated with larger EDs, the absence of a triage nurse, older patients and moderate initial pain intensity.[203]

High levels of ED crowding and long wait times are common in some European countries as demand for services increases: in France, visits to the ED increased by 64% from 1995 to 2005, while in Italy the number of ED visits has recently been increasing by 5% to 6% per year.[204] Overcrowding contributes to delays in patients receiving analgesia.[201] In a retrospective cohort study of patients presenting with severe pain to the ED, 70% experienced delay between triage and analgesia and 49% experienced delayed analgesia after placement in a room/cubicle in the ED.[201] Delays in treatment were independently associated with overcrowding parameters (number of waiting rooms and inpatients, and occupancy rates) and increased as the ED became busier.[201]

Discharge from the ED

Effective communication between the physician and patient is required for optimal management of the patient after discharge from the ED.[205] Before discharge it is essential to evaluate analgesic requirements and prescription. Consider when paracetamol is being used in discharge analgesia that the daily limits of paracetamol are not exceeded. When sending patients home with opioids, ensure that only 2–3 days dosing are provided to mitigate risks of abuse. Similarly, ensure patients are fully informed of the risks and side effects of opioids including dependence, constipation, respiratory depression as well as safe storage and disposal. Patients should also be provided with information about non-pharmacological analgesia such as the use of heat and cold, physical activity and physical therapy. Patients should be provided with written discharge information to reinforce messages and complement verbal instructions.[205] These can come in a variety of formats, from simple written notes to pre-formatted instruction sheets with spaces for patient details and instructions to be added (**Figure 7.1**). The latter are recommended as they can include standardised language that has been reviewed for clarity and simplicity, and the provision of subheadings can help to prompt ED personnel to provide adequate information that covers all relevant topics.[205]

Published recommendations also include the establishment of policies and procedures to promote best practice in communication in the ED, including systems to ensure that discharge instructions are given to all patients upon leaving the ED.[205] Over half of patients who arrive at the ED in pain will still have moderate-to-severe pain at discharge.[206] Emergency physicians therefore have an important role in helping patients to manage pain, even after they have left the ED. Discharge of patients from the ED with limited or no analgesia remains unacceptably high.[206,207] Around three quarters of patients discharged from the ED with a prescription for medication state that they are

satisfied with their pain relief.[208] However, 13% of patients with prescribed analgesics never collect their medication, and unsurprisingly perhaps, these patients report the least satisfaction with their pain control.[208]

Figure 7.1 Sample discharge information sheet

Discharge Information Sheet

Patient name……
This form provides information about your medical care following discharge from hospital.
Please keep this form and take it with you in case you need further care from your primary care physician or hospital.

You were seen today by Drs……..
……

Your diagnosis……..
What you might expect……
Potential complications which may occur……
Return to the Emergency Department if the following occurs……..

Prescribed medication (name, dose, frequency of administration, reason for prescribing)
1……..
2……..
3……..
What to do with your current medication……

Follow up with…….. Contact details……
Follow up within (days/weeks)……..

Instructions given by
Name…… Signature……..

I, the patient, have read and understood these instructions
Name…… Signature……..
Date……..

Education regarding pain management

Pain management is often not prioritised within ED training and education[209] and requires urgent upskilling of emergency personnel to understand the rationale and impact of effective pain assessment and management. One UK study over 3 sites indicated that pain management training was not incorporated into ED induction packages or ongoing ED training, with the exception of nurse triage training, and some condition-specific training, and there was limited awareness of either national or local pain management guidance.[209] Management of pain was often driven by personal healthcare professional experience and preferences rather than evidence-based knowledge and reliance on colleagues for support.[209]

Training does effect change in emergency settings. Evaluation of a training programme indicated that after training paediatric pain assessment and management improved in those with trauma pain compared with before: 94.4% vs 84% ($p<0.001$), and pain medication was prescribed more often ($p<0.001$), however across the groups teenagers and toddlers were less likely to receive analgesia.[141]

The opioid crisis presents a learning opportunity for all healthcare personnel and patients and requires all emergency clinicians to explore other options that optimise and individualise analgesia for each and every patient. There is a need for development, optimisation and implementation of pain assessment and management protocols that enhance patient recovery and reduce the dependency on opioids.

Management of pain – considerations: take home messages

- The last five years have seen the opioid crisis intensify in the USA and Europe, driving the need for alternative and safer pain management strategies in pre-hospital and emergency settings.
- Uncontrolled acute pain in emergency settings has significant physiological (cardiovascular, respiratory, immune, metabolic) and psychological (anxiety, delirium, chronic pain, post-traumatic stress disorder) consequences, and increases healthcare utilisation and system burden.
- Pain is frequently undertreated before hospital arrival, with significant geographic and system variability. Many patients, especially the elderly and children, receive no analgesia despite high pain scores.
- Combining non-opioid medications (e.g. NSAIDs, paracetamol), regional anaesthesia, and non-pharmacological techniques in multimodal analgesia is now central to emergency pain management, reducing opioid reliance and side effects while improving individualised pain control.
- Multimodal analgesia includes non-pharmacological elements including psychological interventions (information sharing, distraction, relaxation techniques) and physical methods (splinting, cooling, positioning) can complement pharmacological treatments, though robust ED-specific evidence is limited.
- For acute mild-to-moderate pain, non-opioid analgesics are recommended as first-line; opioids should be reserved for severe cases and used judiciously within stewardship frameworks.
- When opioids are necessary, use the lowest effective dose for the shortest duration, avoid long-acting or combination opioids, and co-prescribe supportive medications (e.g. laxatives, antiemetics) as needed. Educate patients about tapering and risks.
- Analgesics such as ketamine (IV, IN, nebulised), methoxyflurane, and intranasal fentanyl are effective alternatives to opioids in both pre-hospital and ED settings, with evidence supporting their safety and efficacy.
- Ultrasound-guided nerve blocks offer rapid, effective, and opioid-sparing pain relief in the ED, with a good safety profile and growing evidence for broader use.
- Pain management must be tailored to individual patients, with attention paid to special populations including the elderly, cognitively impaired, children and ethnic minorities who are at higher risk of oligoanalgesia due to systemic biases, communication barriers, and protocol gaps. Targeted strategies are needed to address these disparities.
- ED crowding, lack of standardised protocols, and insufficient pain management training contribute to delays and variability in care.
- Many patients leave the ED with unresolved pain or without appropriate prescriptions. Effective communication, written instructions, and follow-up are essential for ongoing pain management.
- Pain management is underrepresented in emergency medicine training. Enhanced education and protocol implementation are critical for improving outcomes and reducing opioid dependency.
- Overall, emergency pain management must balance prompt, effective relief with minimising opioid risks, using a holistic, evidence-based, and patient-centred approach.

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CHAPTER 8:

Recommendations for acute pain management in emergency settings

Considerations for effective management of acute pain in emergency settings

In the pre-hospital or ED setting pain management should be straightforward to administer and be patient- and condition-specific. In all cases it should be preceded by pain assessment and recording of pain scores. This guideline handbook, and in particular this chapter, have been developed to provide clear updated guidance on pain management approaches for both adults and children. The recommendations in this chapter do not cover palliative care or discharge analgesia from either the pre-hospital or ED setting.

This chapter provides an overview of treatment options for patients experiencing acute or breakthrough pain. The aim is to provide flexible recommendations for pain management in adults and children that allow national, regional and institutional flexibility based on drug availability and individual settings (both pre-hospital and ED). An overview of pain management principles is provided here, prescribing caveats for special populations (e.g. children, renal or hepatic impairment, specific comorbidities, drug seeking behaviour) can be found in **Chapter 7**.

The content contained in this chapter is intended for use by all emergency personnel including ED physicians, nurses and paramedics who have relevant administration authority. The recommendations give an overview of potential analgesic medications that may be used to manage pain depending on its severity. Practitioners should choose medication within their appropriate administration rights and within their scope of professional expertise and practice and accept clinical/legal responsibility for their administration decisions.

Updated recommendations for management of acute pain in the emergency setting

The changing landscape over the last five years including technological advances because of the COVID-19 pandemic, the opioid crisis, an ageing population and the continued pressure on emergency services requires an update of approaches to acute pain management in the emergency setting.

This updated guideline has evolved from the original with a view to providing recommendations that are flexible across all healthcare settings, regardless of medication access, and enable ED personnel to implement pain management strategies that will remain relevant for the long-term. The aim is to enable clinicians to modify their approach depending on the individual patient.

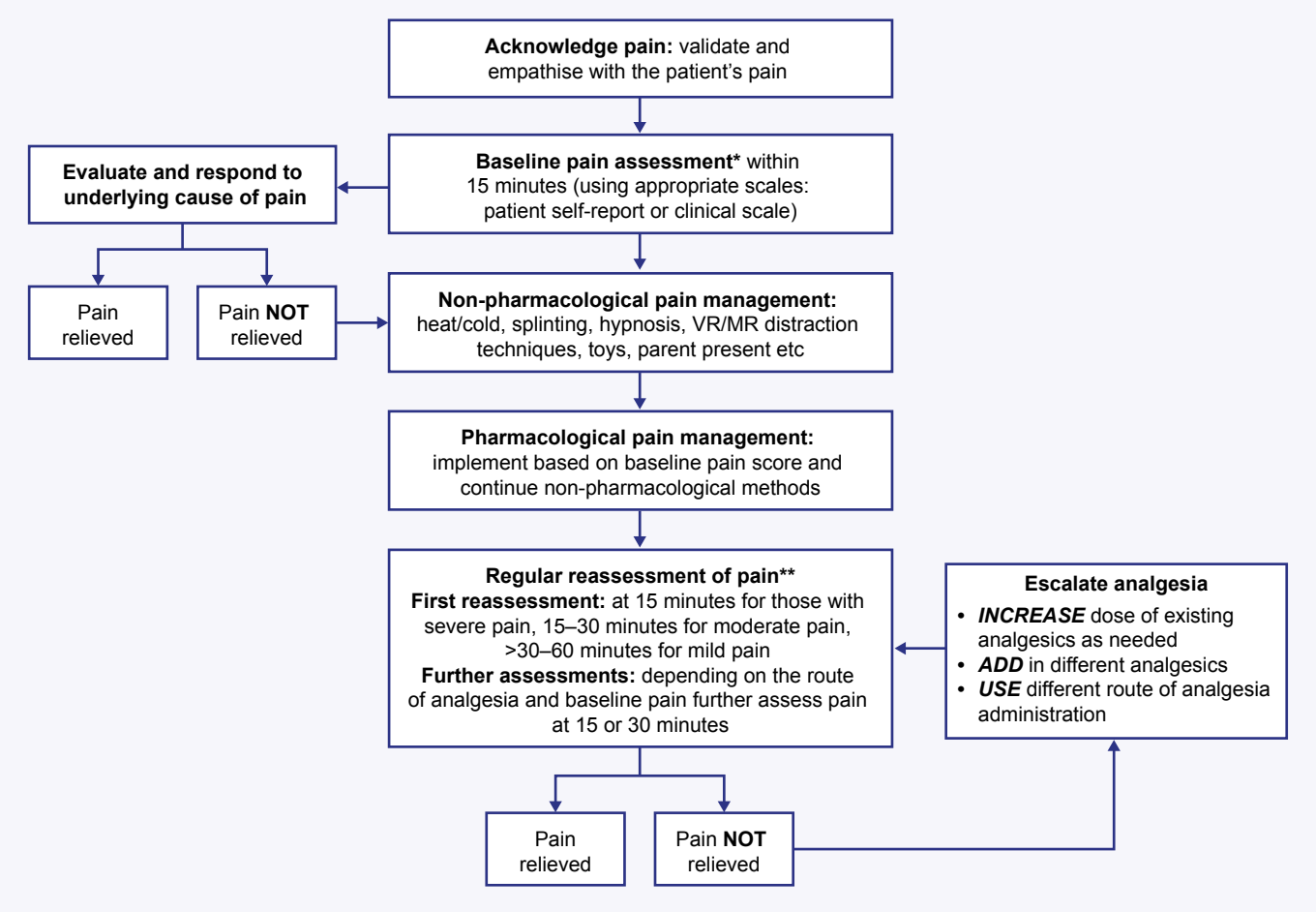
The PICO research question determined for this update was to examine the effectiveness of multimodal pain management strategies for patients entering an emergency setting with a pain score of NRS ≥4 or VAS ≥4 (on a 0–10) or ≥40 (on a 0–100 scale).

2025 EUSEM recommendations for management of acute pain in emergency settings

Given the variety of medication availability across Europe, the EUSEM recommendations have been developed with a range of flexible alternative options to meet the needs of individual institutions and settings. Before using the recommendations in this chapter, it is incumbent on the user to review their analgesic choices against the needs and characteristics of the individual patient.

Recommendations for the management of acute pain in emergency settings in adults and children are provided in **Figures 8.1–8.3**.

Figure 8.1. Acute pain in emergency settings patient pathway



MR, mixed reality; VR, virtual reality.

FOOTNOTE:

***Pain assessment:** where possible use patient self-report. Consider the pain scoring tool used to ensure it meets the needs of the patient, particularly those who are unable to self-report effectively such as children and those with cognitive impairment. Where possible use tools that are multidimensional but easy to implement in a busy emergency environment.

****Pain reassessment:** time of reassessment is determined by the degree of baseline pain and analgesic options adopted. **ADULTS & CHILDREN:** consider first reassessment of pain as follows: for severe baseline pain at 15 minutes, baseline moderate pain 15–30 minutes and >30–60 minutes for mild pain. On reassessment, if pain reduction is not evident then escalate analgesia and reassess. Route of analgesia administration should also be considered. For IV, IN and SL administration reassess pain score at 15 minutes. For IM and PO administration assess pain at 30 minutes.

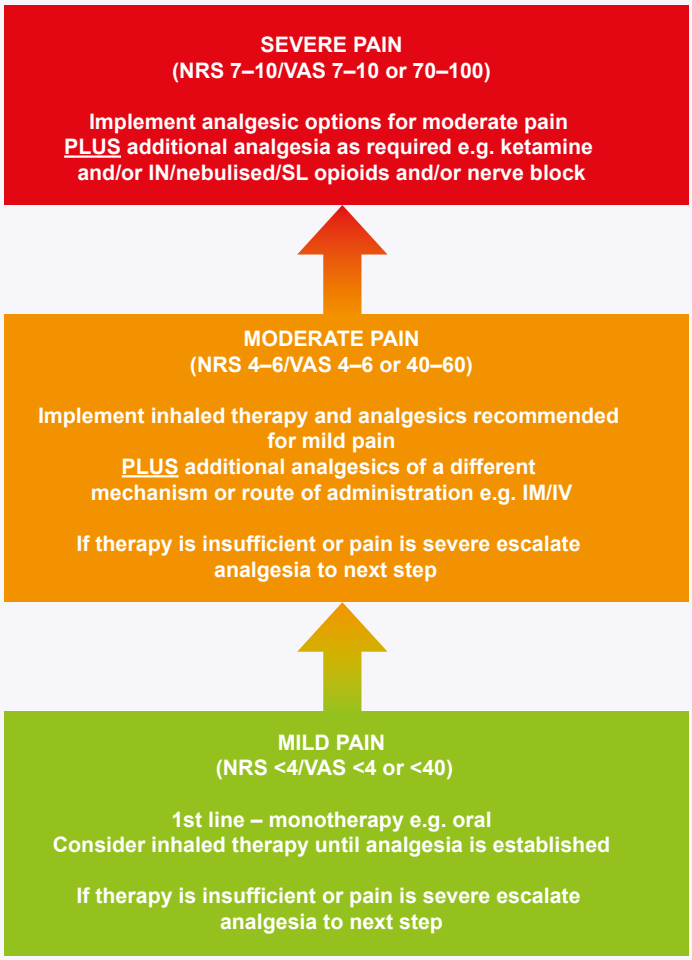
Figure 8.2. Management strategy for acute pain in emergency settings

Emergency setting specific recommendations

- Develop analgesic protocols that embrace a multimodal, multidisciplinary approach so that effective analgesia (non-pharmacological and pharmacological) is provided as soon as possible in the patient's journey through emergency care
- When additional analgesia is needed, consider a drug with another mechanism of action, do not rely on dose escalation alone

Patient-specific recommendations

- Evaluate baseline pain (NRS/VAS/FACE/CRIES etc) considering the capabilities of the patient*
- Use multimodal pain assessments where available for implementation
- Treat the underlying cause of pain
- Consider non-pharmacological pain relief
- If non-pharmacological methods alone are insufficient or pain is severe, escalate to pharmacological analgesia
- Manage patients' expectations where improvement rather than elimination of pain is a more realistic goal
- Re-evaluate mild or moderate pain at 30 minutes post-implementation of analgesia (unless patient visibly in increasing pain)**
- Re-evaluate severe pain at 15 minutes post-implementation of analgesia**
- Escalate analgesia based on regular pain assessments and pain scores, individualised to the patient; ***NOTE:*** *whilst oral, intranasal, inhaled or IV routes of administration are preferred, depending on patient circumstances; when opioids are required IM, IO or SC routes of administration may need to be considered but should be considered as last resort when other routes are not available*



CRIES, crying, requires oxygen, increased vital signs, expression, sleeplessness; IM, intramuscular; IN, intranasal; IO, intraosseous; IV, intravenous; NRS, numerical rating scale; SC, subcutaneous; SL, sublingual; VAS, visual analogue scale.

FOOTNOTE:

***Pain assessment:** where possible use patient self-report. Consider the pain scoring tool used to ensure it meets the needs of the patient, particularly those who are unable to self-report effectively such as children and those with cognitive impairment. Where possible use tools that are multidimensional but easy to implement in a busy emergency environment.

****Pain reassessment:** consider first reassessment of pain as follows: for severe baseline pain at 15 minutes, baseline moderate pain 15–30 minutes and >30–60 minutes for mild pain. On reassessment, if pain reduction is not evident then escalate analgesia and reassess. Route of analgesia administration should also be considered. For IV, IN, inhaled and SL administration reassess pain score at 15 minutes. For IM and PO administration assess pain at 30 minutes.

Figure 8.3a. Treatment options within the management strategy for acute pain in ADULTS (≥16 years) in emergency settings

SEVERE PAIN (NRS 7–10/VAS 7–10 or 70–100)	**Analgesic options in ADDITION to those for moderate pain if needed (ensure new drug is of a different class):** IN/SL/buccal/nebulised opioids (fentanyl, sufentanil) IV opioids (morphine, fentanyl, sufentanil) IN/nebulised/IV ketamine (potential for combination with antipsychotics e.g. haloperidol, diazepam or midazolam) Nerve block (bupivacaine/ropivacaine)
MODERATE PAIN (NRS 4–6/VAS 4–6 or 40–60)	**Analgesic options in ADDITION to those for mild pain if needed (ensure new drug is of a different class):** Topical lidocaine INH nitrous oxide Oral opioids INH methoxyflurane IV paracetamol IV NSAIDs (ketorolac) IN/nebulised/IV ketamine (potential for combination with antipsychotics e.g. haloperidol, diazepam or midazolam) IV/IM metamizole Nerve block where appropriate
MILD PAIN (NRS <4/VAS <4 or <40)	**Analgesic options:*** Topical or oral NSAIDs (e.g. ibuprofen, diclofenac) Oral paracetamol

IM, intramuscular; IN, intranasal; INH, inhaled; IV, intravenous; NRS, numerical rating scale; NSAIDs, non-steroidal anti-inflammatory drugs; SL, sublingual; VAS, visual analogue scale.

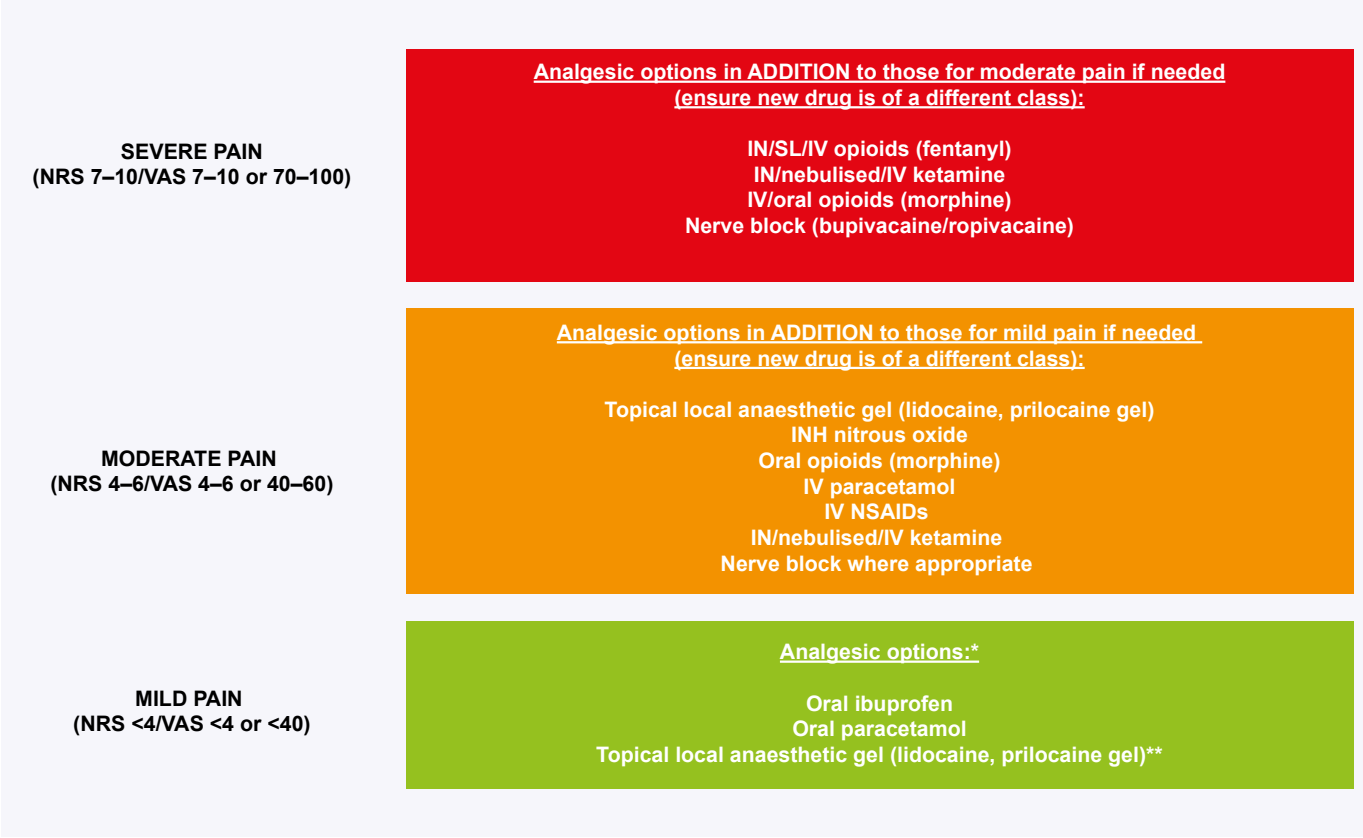
FOOTNOTE:

*Consider the use of inhaled therapy i.e. nitrous oxide or methoxyflurane while other methods of analgesia are being established

Specific considerations:

- Codeine and tramadol are not recommended because of their significant pharmacological limitations, safety concerns and the availability of superior alternative medications.
- The use of the opioid oxycodone is discouraged and not recommended given its association with higher rates of euphoria than other opioids.
- Metamizole is associated with life-threatening agranulocytosis and should be used with caution.
- Ensure availability of naloxone if opioids are used.
- For patients who receive NSAIDs, administration of a second different NSAID is contraindicated e.g. if a patient receives ibuprofen, then other NSAIDs like diclofenac or ketorolac should not be used.
- If analgesia is not sufficient, escalate therapy using drugs from another class and/or dose escalation – drugs from the same class should not be used in combination.
- Patients should be discharged from the emergency setting with minimal opioids, no more than 2–3 days dosing to minimise the risk of addiction.
- Escalate analgesia based on regular pain assessments and pain scores, individualised to the patient; ***NOTE:*** *whilst oral, IN, inhaled or IV routes of administration are preferred, depending on patient circumstances when opioids are required IM, IO or SC routes of administration may need to be considered when other routes are not available or not feasible.*
- IM administration should be individualised to the patient and used when oral, IN, inhaled and IV access is not available or difficult. The use of IM delivery is strongly discouraged due to painful administration, unpredictable absorption, slow onset to effect, risk of local complications and superior alternatives and should be reserved only for exceptional circumstances when other routes are impossible.

Figure 8.3b. Treatment options within the management strategy for acute pain in CHILDREN (>1–≤15 years) in emergency settings



IM, intramuscular; IN, intranasal; INH, inhaled; IV, intravenous; NRS, numerical rating scale; NSAIDs, non-steroidal anti-inflammatory drugs; SL, sublingual; VAS, visual analogue scale.

FOOTNOTE:

*Consider the use of inhaled therapy i.e. nitrous oxide while other methods of analgesia are being established

**When planning analgesia for paediatric patients, consider local anaesthetic cream/gel (lidocaine or lidocaine/prilocaine or tetracaine) to facilitate IV administration. NOTE: onset of effect of anaesthetic cream/gel requires from 30 minutes up to 60 minutes lead time.

Specific considerations:

- Ensure availability of naloxone if opioids are used.
- Consider anti-emetics as adjunct to opioids: ondansetron to overcome nausea and reduce vomiting.
- For patients who receive NSAIDs, administration of a second different NSAID is contraindicated e.g. if a patient receives ibuprofen, then other NSAIDs should not be used.
- If analgesia is not sufficient, escalate therapy using drugs from another class and/or dose escalation – drugs from the same class should not be used in combination.
- Codeine is contraindicated in children and is not recommended.
- Methoxyflurane (Penthox) has demonstrated efficacy and safety in paediatric population, particularly for the management of acute traumatic pain in pre-hospital and emergency settings.[78,79] Despite this robust evidence base, the lack of formal regulatory approval for pediatric use of Penthrox in wider Europe remains a significant barrier, limiting its broader implementation across European emergency departments and prehospital systems. As such, use of methoxyflurane in children and adolescents is off-label. Methoxyflurane has very recently been approved for use in children in Ireland,[80,81] and whilst it remains off-label in wider Europe, its use in children aged 6 and over who can cope with instruction should be considered.

To provide the flexibility required in busy, diverse emergency settings the recommendations are based on an agreed set of guiding principles with the following additional considerations:

- **Regular training** for all emergency personnel to ensure effective and timely intervention. With effective training and support pain management strategies can be implemented early, even at triage, by a range of clinical personnel.
- **Effective analgesia education in pain assessment and management for clinicians, nurses, and paramedics in emergency settings is crucial** for addressing oligoanalgesia and improving patient outcomes. Standardised protocols enable timely pain relief, particularly for vulnerable populations including children, the elderly and those with complex pain histories. Specific training programmes enhance assessment skills using validated pain scales, promote evidence-based multimodal approaches, and reduce variability in clinical practice. Educational interventions improve both clinical competency and patient satisfaction while ensuring safe analgesic administration across diverse emergency presentations.
- **Development of manageable and effective multimodal acute pain management protocols** for all emergency personnel to mitigate uncontrolled pain.
- **Clinicians should evaluate how distress is contributing to a patient's pain experience**, take measures to address their pain empathically, acknowledging it and demonstrating a willingness to understand their experience.
- **Documentation of pain intensity pre- and post-interventions**. Baseline and regular pain assessments should be undertaken and documented using tools applicable to the individual in pain. Unidimensional scales such as NRS and VAS remain the norm, but EUSEM recommend the consideration of multidimensional pain scales such as the BPI short form that can capture all facets of the patient's experience of pain. Consider specific assessment and behavioural tools for the very young, for patients who are unable to communicate effectively because they are non-verbal, cognitively impaired patients etc. (see **Chapter 6** for an overview of pain assessment tools in clinical practice).
  - NRS, VRS and VAS are simple to use and validated for the ED. Of these NRS may be the simplest to use in busy emergency settings.[1,2]
  - For patients who are not alert or verbally communicative, or for young children unable to self-report consider the FLACC and FACES scales which are recommended for use in young children and those with no and limited ability to communicate.[3–5]
  - For babies tools such as CRIES along with FLACC and FACES should be considered.[6]
  - Whilst the use of validated pain scales has been shown to be effective in the elderly or those with cognitive impairment, additional tools such as the PAINAD scale should be considered (see **Chapter 3**).[7,8]
  - Where possible multidimensional tools such as the BPI short form should be considered as appropriate options in emergency settings.[9]
  - Frequency intervals for pain assessment post-baseline should be determined by baseline pain levels and the route of administration of analgesic medication, being aware that administration time and onset to pain relief varies by administration route: IN, SL, inhaled, IV and IM.
  - When evaluating pain after an intervention, determine if the desired effect has been achieved, if not then escalate pain management.
- **Effective communication, which should be documented, with patients and their caregivers** to set realistic expectations for their pain management, gaining their input through shared division-making and exploring 'success' in relation to pain control e.g. to eat, sleep, ambulate, or participate in care despite residual pain (see **Chapter 7**).
- **Implementation of non-pharmacological pain management strategies for all patients** as appropriate. This may involve techniques such as splinting, immobilisation, heat/cold, techniques to distract patients from their pain e.g. VR, MR and for children additional distraction including toys and techniques such as play (see **Chapter 4** for an overview of non-pharmacological analgesia).
- **If pharmacological analgesia is required, ensure that there are no contraindications** to medications before administration and ensure that all medications administered are clearly documented (see **Chapter 5** for an overview of pharmacological analgesia).

- **First-line analgesia should be determined by the patient's baseline pain and pain reassessed at a pre-determined interval**, with escalation or de-escalation using multimodal analgesia with CERTA principles in line with the established WHO analgesic ladder[10,11] (see **Chapter 7**).
- **Consideration of the analgesic administration route**, based on pain severity, patient characteristics, staff training levels, and clinical urgency rather than defaulting to traditional IV opioid approaches. Choice should meet the needs of the individual patient and the required speed of onset for analgesia. Evidence supports non-opioid multimodal strategies as equally effective with superior safety profiles for most emergency pain scenarios (see **Chapter 5** and **Chapter 6**). EDs implementing comprehensive pain management protocols demonstrate improved outcomes when multiple routes are available. As in our previous recommendation, EUSEM continues to advocate strongly for a multimodal approach to analgesia utilising multiple routes of administration and analgesics. It should be noted that that each route of administration requires staff training. Training complexity hierarchy moves from lowest to highest: oral → topical → intranasal → subcutaneous → sublingual/buccal → intramuscular → nebulised → intraosseous → intravenous → nerve blocks. Ease of administration for analgesia is simplest for oral, topical, intranasal, inhaled, sublingual increasing in difficulty to IV. For opioids specifically, administration by other routes such as SC, IM or IO should only be considered when other routes are unfeasible or impractical based on the patient's individual circumstances. Oral and intranasal routes have near-universal applicability, while nerve blocks require specialised expertise but provide superior analgesia for appropriate indications.
  - **Oral.** Preferred where possible. Oral administration requires minimal specialised training and represents the simplest, most cost-effective approach to analgesic delivery. Healthcare providers need basic knowledge of appropriate dosing and contraindications, making it suitable for all staff levels including basic emergency medical technicians. Typically reliable in most cases, it does have a slower onset to effect than IV. Oral analgesics demonstrate slower onset profiles compared to parenteral routes.
  - **Topical analgesia/anaesthesia.** Topical anaesthetics require minimal training in application techniques, wound assessment, and appropriate agent selection. Simple application methods make this accessible to all healthcare providers with an onset to analgesia of 30–45 minutes. Topical analgesia or anaesthesia is limited to superficial wounds and lacerations and other local pain. Topical anaesthesia e.g. topical lidocaine gel/cream (lidocaine 4%) or lidocaine plus prilocaine gel/cream (EMLA™), is particularly useful for paediatric patients requiring onward analgesia using more invasive routes of administration e.g. IM, IV or for patients who have a fear of needles.
  - **Intranasal (IN).** IN administration requires basic training in nasal anatomy, proper device positioning, and dosing calculations. Training typically involves 1–2 hour educational sessions covering technique, contraindications, and adverse event recognition. The non-invasive nature eliminates venipuncture skills requirements. IN fentanyl demonstrates rapid absorption with therapeutic levels reached within 2 minutes, time to maximum concentration of 7 minutes, and analgesic duration comparable to that of IV administration. Paediatric studies show effective pain reduction at 5, 10, 20, and 30 minutes post-administration. IN administration is particularly valuable for paediatric patients, those with difficult IV access, or situations requiring rapid non-invasive analgesia. Contraindications include nasal obstruction, bleeding disorders, or facial trauma affecting nasal passages.
  - **Subcutaneous (SC).** Better tolerated than IM administration, it can be used intermittently or in palliative settings continuously. Only reliable if peripheral circulation is adequate and may be useful when the oral route is not feasible. Like IO and IM administration, consideration of SC administration of opioids, should be individualised to the patient and used when oral, IN, inhaled, and IV access is not available or difficult. SC administration is limited by local irritation, is contraindicated in patients with evidence of oedema, inflammation or skin damage at site of planned administration and is unsuited for use in cachectic, or dehydrated patients. **It should also not be used in patients with significant peripheral hypoperfusion due to risk of impaired drug absorption.** In the experience of the expert panel SC administration in paediatric patients is rarely useful, particularly in a busy ED where its use is not feasible and may prove painful and anxiety-inducing to children.

Other analgesic routes for children including oral, IN and IV may be more acceptable to patients and more straightforward to implement for HCPs.

- **Sublingual (SL)/buccal.** SL and buccal administration requires minimal training focusing on proper tablet/film placement, patient positioning, and swallowing avoidance. Training complexity approaches oral administration levels. SL fentanyl demonstrates onset within 5–15 minutes with peak effect at 15–30 minutes. Buccal acetaminophen achieves analgesia onset from 15 minutes, significantly faster than oral preparations. SL and buccal dosing is suitable for conscious patients capable of following instructions to maintain medication positioning. Particularly valuable in patients unable to swallow but requiring faster onset than oral routes. This route of administration is contraindicated in those with oral lesions, altered mental state that precents cooperation and in those with severe xerostomia.
- **Intramuscular (IM).** IM administration was historically very commonly used but is now discouraged. It should be considered the administration route of last resort except for specific circumstances. Like IO and SC administration, consideration of IM administration of opioids, should be individualised to the patient and used when oral, IN, inhaled and IV access is not available or difficult. However, in hostile environments (e.g. helicopter emergency medical services [HEMs] call outs) IM is the preferred route of analgesic administration ready for effective patient evacuation and the de facto route for mass casualty management and can facilitate IV administration once patients are extricated.. The use of IM delivery is strongly discouraged due to painful administration, unpredictable absorption, slow onset to effect, risk of local complications and superior alternatives and should be reserved only for exceptional circumstances when other routes are impossible. Do not use IM administration for chest pain due to the possibility of pain being due to cardiac origin and potential for future use of thrombolytic medicines.
- **Nebulised/inhaled.** Nebulised administration requires training in device setup, dosing calculations, and patient positioning. Nebulised or inhaled analgesics are suitable for conscious patients with intact respiratory function. Contraindications of this route include respiratory depression, pneumothorax or otitis (for nitrous oxide specifically), or patient altered mental state. Nitrous oxide/oxygen requires specific training in self-administration techniques and contraindication recognition. Nitrous oxide demonstrates onset within 20 seconds with peak effect at 3–5 minutes and immediate reversibility upon discontinuation. It is useful for procedural analgesia in conscious patients who require self-controlled analgesia where rapid reversibility is desirable. Nebulised fentanyl shows onset within 5–10 minutes with sustained effect. Inhalation of methoxyflurane using the specific Penthrox® inhaler is a quick, well tolerated and effective method of analgesia for conscious patients without any changes in consciousness, circulation and respiration.
- **Intraosseous (IO).** IO administration may be of use in severe emergencies or life-threatening situations when other routes of administration are not available, but it must be noted that in conscious patients IO administration is very painful and may require lidocaine infiltration to mitigate pain. Like IM and SC administration, consideration of IO administration of opioids, should be individualised to the patient and used when oral, IN, inhaled and IV access is not available or difficult for example in trauma, paediatric emergencies, or cardiac arrest situations. Contraindications include fracture at insertion site or infection overlying target area.
- **Intravenous (IV).** IV administration has a fast onset, with reliable outcomes and is excellent for acute or titratable analgesia but may be less practical in out of hospital settings. IV administration requires advanced training in venipuncture techniques, sterile procedures, and recognition of complications including infiltration and phlebitis. IV route provides the fastest analgesic onset, with fentanyl achieving effect within 1–2 minutes and morphine within 5–10 minutes. This rapid onset enables precise titration and immediate pain relief in critical situations. IV access is indicated for severe pain requiring rapid onset, hemodynamically unstable patients, or those requiring precise drug titration. Limitations include difficulty establishing access in hypovolemic, paediatric, or technically challenging patients.
- **Nerve block.** Ultrasound-guided nerve blocks require extensive training including ultrasound image interpretation, needle manipulation skills, local anaesthetic pharmacology, and complication management. Nerve blocks demonstrate onset within 5–15 minutes depending on technique and agent used, with duration

of 6–12 hours. Nerve blocks are indicated for moderate to severe pain or specific traumatic injuries as well as specific anatomical pain patterns, and patients requiring prolonged analgesia. Nerve blocks are particularly useful in trauma pain, and in patients intolerant of systemic opioids, and situations requiring motor function preservation. Nerve blocks are contraindicated in those with infection at the injection site, coagulopathy or patient refusal.

- **For patients being discharged to home provide effective post-discharge information and analgesia** (see **Chapter 7**).
- **Audit emergency pain management practice at least annually** to determine efficacy and areas for improvement (see **Chapter 6**).

Analgesic prescribing in adults and children

FOR ALL PATIENTS: assess each patient for contraindications for all drugs planned for use, including simple analgesics. Consult the Summary of Product Characteristics for each medication available in your country or from the European Medicines Agency (EMA) as required, for further information and an overview of drug-drug interactions.

General principles for all patients

- Do not use intravenous (IV) opioids in combination with other IV opioids because of the risks of sedation and respiratory depression.
- When administering opioids ensure that naloxone is available for reversal and ready to use as required if clinically significant sedation or respiratory depression occurs.
- Only prescribe second-line NSAID analgesia (e.g. diclofenac or ketorolac) in patients who have not received previous NSAIDs e.g. ibuprofen.
- When combining strong analgesics such as ketamine with opioids, to decrease the risk of respiratory depression consider strategies that provide ketamine first (up to the maximum permitted dose) and then titrate opioids to appropriate analgesia rather than the other way around.

Off-label use of medications, including analgesics, is common practice especially in patient groups not represented in clinical trials. This practice can improve patient care by addressing unmet needs, but brings legal, safety, and ethical considerations. Robust evidence or best clinical practice must be considered to justify use, patients and relatives should be informed of off-label use of any medicines and their potential benefits and harms, and prescribers should understand they are liable for adverse events.

Dosing considerations for adults (≥16 years)

- **Codeine: not included as part of EUSEM recommendations because of its significant pharmacological limitations, safety concerns and availability of superior alternative medications. However, it is recognised that in some countries the use of codeine for acute pain is advocated and, in these instances, local recommendations should be considered.** Codeine should be considered a pro-drug of morphine with no analgesic activity until it is metabolised to morphine. Its use is limited by individual patient CYP2D6 metabolism which may result in differing effects. Patients may be poor, intermediate, extensive or ultra-rapid metabolisers of codeine which impacts patient outcomes.[12,13] CYP2D6 poor metabolisers (approximately 7% of Caucasians) experience minimal to no analgesic benefit from standard doses. Conversely, ultra-rapid metabolisers (1–2% of the population) face increased toxicity risks from excessive active metabolite formation. The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends avoiding codeine and morphine in poor and ultra-rapid metabolisers, advocating for alternative analgesics unaffected by CYP2D6 phenotype.[13,14] Phenotyping within a busy emergency setting is largely unfeasible. Efficacy of codeine compared with paracetamol and ibuprofen is questionable with a 2017 study finding no clinically meaningful differences in pain score between the three medications.[15] Codeine is also prone to drug-drug interactions and an analgesic ceiling effect. Its use in emergency settings may be limited, but it is recognised that in some countries, codeine is a lynchpin for emergency analgesia. If codeine is used, monitor for analgesic efficacy and use alternatives if reduced efficacy is observed. Codeine should not be used in breastfeeding patients.[16] Indicated for use in patients aged ≥12 years, in adults oral doses of 30–60 mg may be considered up to maximum adult dose of 240 mg/day.[17] The duration of codeine treatment should be limited to 3 days.[17]
- **Diazepam:** available as an oral solution or for injection and is used to supplement analgesia to provide sedation and anti-anxiety effects.[18,19]
- **Fentanyl:** for IN, nebulised or IV administration dosing should be started at 50 µg if possible and may be repeated after initial dosing to a maximum dose of 200 µg or by continuous infusion according to local protocols; if IN fentanyl proves insufficient follow with IV fentanyl or IV morphine.[20] Fentanyl is also available in buccal and SL formulations which are indicated for use in breakthrough cancer pain, but are used off-label in acute pain management.[21,22]
- **Haloperidol:** available as an oral solution or injection formulations and is used to supplement analgesia.[23,24]
- **Ketamine:** indicated for use when painful extrication from the emergency scene is required, in moderate-to-severe pain ahead of opioids, or when opioids such as morphine or fentanyl prove insufficient. IV dosing of 0.1 mg/kg is recommended which can be repeated but not more frequently than 10 minutes. IN dosing of 0.7 mg/kg can be considered with the potential to provide subsequent dosing of 0.3–0.5 mg/kg at not more than 15 minutes or IM dosing of 0.5–1 mg/kg with the option to repeat dosing once. Please note that ketamine is associated with salivation so careful airway management is important.[25] Avoid use in pregnancy.[25]
- **Lidocaine:** available for injection and topical use. Injectable lidocaine is indicated for use for regional block in adults and children >1 year of age.[26] The lowest concentration and smallest dose producing the required effect should be given.[26] The maximum single dose of lidocaine when given with adrenaline is 500 mg.[26] Lidocaine is also available in a medicated plaster form, indicated for the relief of neuropathic pain.[27]
- **Metamizole:** may be administered as an adjunct to paracetamol in moderate pain at an oral dose of 8–16 mg/kg or slow IV infusion of 1 g, but the risks of serious adverse events mean it cannot be considered for first-line treatment.[28,29] Serious adverse events include severe agranulocytosis, allergy and anaphylaxis, but its use may be beneficial in emergency care in hostile environments such as entrapment or inhospitable environments such as mountain rescue.
- **Methoxyflurane:** indicated for use in adult patients with moderate-to-severe acute trauma. One bottle of methoxyflurane in the Penthrox inhaler will provide up to 30 minutes analgesia with continuous use and longer with intermittent use.[30] A second bottle may be added to the Penthrox inhaler if required for extended analgesia,

further dosing is contraindicated within 24 hours.[30] The use of methoxyflurane should be considered in inhospitable environments where patients are difficult to reach e.g. mountain rescue, entrapment or multiple casualties.[30]

- **Midazolam:** typically used to induce sleep or to stop prolonged convulsive seizures but is used to supplement analgesia for its sedative effects and anxiolysis. It is available as IV initial adult dose 0.4 ml midazolam 5 mg/ml (equivalent 2 mg midazolam) over 30 seconds, IM single injection of 0.07–0.1 mg/kg bodyweight 30–60 minutes before procedure,[31] SL/buccal indicated for patients >3 months in a hospital setting with dosing from 2.5 mg to 10 mg based on age,[32] oral solution 0.25–0.5 mg/kg administered 15–30 minutes before intervention,[33] IN administration (not available in all European countries) first dose by bodyweight from 2.5–5 mg with a second dose possible no earlier than 10 minutes after the first dose.[34]
- **Morphine:** for IV administration at doses of 2.5–15 mg administered over 4–5 minutes, SC/IM 5–20 mg (at 10 mg/time) and repeated up to every 4 hours, epidural 3.5–7.5 mg per day with potential to increase dose by 1–2 mg/day, or can be used as part of Patient Controlled Analgesia (PCA) system 0.2–1 mg maximum demand dose with a lockout period of 5–10 minutes.[35,36] Dosage of morphine should be individualised to the patient's pain, response to opioids and patient's opioid tolerance.[35,36] For oral administration, morphine is available in tablet, orodispersible and solution formulations.[37–40] For analgesia in the emergency setting immediate release over sustained release is preferred.[38,40] Morphine oral solution should be dosed at 10–20 mg (5–10 ml) every 4 hours to a maximum dose of 120 mg/day.[37] Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with morphine in order to minimise the risk of addiction and drug withdrawal syndrome.[35,36]
- **Nerve block ropivacaine:** ropivacaine 2 mg/ml for infusion is indicted for pain management in adults and children aged >12 years. It can be dose continuously or by intermittent bolus injections, as a field block, peripheral nerve block or caudal epidural block.[41] It should be used with caution in patients with hepatic impairment.[41]
- **Nerve block bupivacaine:** bupivacaine 2.5 mg/ml for infusion is indicted for pain management in adults and children aged >12 years.[42] The dosage varies and depends upon the area to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance and the technique of anaesthesia used.[42] The lowest dosage needed to provide effective anaesthesia should be administered. In most instances a single dose will be appropriate.[42]
- **Nitrous oxide:** a foundational analgesic for emergency settings, and is indicated for the short-term relief of pain.[43] Nitrous oxide should not be used for more than a total of 24 hours, or more frequently than every 4 days, without close clinical supervision and haematological monitoring, and should not be used in any patient where there is suspicion of bodily gas entrapment e.g. following underwater diving, air embolism.[43] It should be noted that nitrous oxide is subject to abuse and is a driver of physical harm including death.[44] As recommended by the Royal College of Emergency Medicine, patients presenting to emergency settings with neurological abnormalities without obvious cause should be reviewed for nitrous oxide toxicity.[45]
- **NSAIDS:** first-line simple analgesics, NSAIDs e.g. ibuprofen, diclofenac, ketorolac etc. have broad applications alone in mild pain and as part of combination therapy for moderate pain, and are available in IV, oral and topical formulations.[46-50]
- **Paracetamol:** a first-line simple analgesic, paracetamol has broad application alone in mild pain and as part of combination therapy for moderate pain.[51] For adults and children aged >16 years, dosing is two 500 mg tablets every 4 hours to a maximum of 8 tablets in 24 hours. Dosing should only be continued for 3 days. Dosing for paracetamol infusion is determined by patient weight and also by presence of additional risk factors for hepatotoxicity.[52,53] It should be used with care in patients with renal or hepatic impairment.[54] Paracetamol suppositories (1,000 mg) are also available and should be dosed at 1 suppository every 4–6 hours up to a maximum of 4 suppositories in 24 hours.[55] Liver damage has been reported in patients following dosing of >10 mg, and ingestion of ≥5 mg paracetamol may cause liver damage in patients with risk factors.[51]
- **Sufentanil:** dosage is one tablet of SL sufentanil 30 µg provided as needed by the patient with a dosing interval not shorter than 1 hour, to a maximum dose of 360 µg/day and use should not exceed 48 hours.[56,57] Sufentanil is contraindicated in patients with significant respiratory or pulmonary compromise.[56]

- **Tramadol: not included as part of EUSEM recommendations because of its significant pharmacological limitations, safety concerns and availability of superior alternative medications. However, it is recognised that in some countries the use of tramadol for acute pain is advocated and, in these instances, local recommendations should be considered.** Tramadol poses unique neurological risks by lowering seizure threshold through multiple mechanisms including sodium channel blockade, serotonin and norepinephrine reuptake inhibition, and NMDA receptor antagonism. A seizure rate of 58% has been reported among tramadol users, a risk that is increased >3-fold in patients with a prior seizure history.[58–61] The unpredictable nature of seizure occurrence makes tramadol particularly problematic in emergency settings where rapid patient turnover limits extended monitoring capabilities. Tramadol also carries a risk of serotonin syndrome, when coadministered with other medications such as selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and triptans. ED case reports document serotonin syndrome from tramadol alone, presenting with hyperthermia, rigidity, myoclonus, and autonomic instability.[62] The unpredictable onset and potentially fatal course make tramadol unsuitable for emergency use where comprehensive medication reconciliation may not be possible.

Dosing consideration for children aged >1 year to ≤15 years

- **Codeine: not included as part of EUSEM recommendations because of its significant pharmacological limitations, safety concerns and availability of superior alternative medications.** A recent clinical practice guideline recommendation reiterates current EMA guidance that codeine should NOT be prescribed in patients <12 years, or adolescents aged 12–18 years who have obesity, obstructive sleep apnoea or severe lung disease.[16,63]
- **Fentanyl:** *see prescribing procedures within your region or institution for more details.* Dosing of fentanyl by the IN route is recommended at 0.0015 mg/kg initial dose (from 0.0015 mg in those weighing >10 kg up to 0.075 mg for those weighing >50 kg), with the option for a second dose of 0.001 mg/kg (from 0.001 mg in those weighing >10 kg to a maximum of 0.05 mg in those weighing >50kg) to be prescribed no sooner than 10 minutes after the initial dose in children who are awake or easily roused.[64] If IN fentanyl proves insufficient, follow with IV fentanyl or IV morphine.[64] For IV administration in those with spontaneous respiration aged 2–11 years, give an initial dose of 0.001 mg/kg with the option for a supplemental dose of 0.001–0.00125 mg/g/kg but not before >10 minutes have elapsed after initial dosing.[20]
- **Ketamine:** first IV dose 0.1 mg/kg which may be repeated once only not <10 minutes after initial dosing as needed.[65,66] IN doses of 1 mg/kg may be administered for patients weighing >10 kg (10 mg) through to those weighing 60 kg (60 mg), with another 0.5 mg/kg administered as a top up dose as required.[66] Patients should be monitored for 30 minutes after administration.[66]
- **Lidocaine:** available for injection and also as a topical solution which is useful for children when removing foreign bodies from the nose or in preparation for laryngoscopy.[70]
- **Topical lidocaine:** consider local anaesthetic creams and gels for children with mild to moderate pain and for the placement of more invasive analgesic routes including IM or IV.[71,72] Suitable gels include 4% lidocaine LMX and lidocaine/prilocaine gel.[71,72] To use overlay a suitable vein with the gel and then cover the area with an occlusive dressing for a minimum of 20 minutes up to 60 minutes.[71,72] Lidocaine 2.5%/prilocaine 2.5% is licensed for use in children aged >1 year.[71] Lidocaine 4% w/w gel is indicated for use in children aged >1 month with only 1 g of cream recommended for use in children below the age of 1 year (1 g cream equates to approximately 5 cm from a 5 g tube and 3.5 cm from a 30 g tube).[72] Lidocaine 4% gel should not be reapplied for 12 hours once it is removed, and no more than 2 doses per 24 hours are permitted.[72]
- **Methoxyflurane:** not currently licensed for use in children in Europe, but is used off-label in many countries.[73,74]
- **Morphine:** for IV administration morphine should be dosed at 0.05 mg/kg, with the option for subsequent dosing at not <2 minutes intervals as needed and may be delivered to a maximum dose of 0.1 mg/kg. Oral morphine

50–200 µg/kg is recommended for children with doses based on bodyweight.[66] IV opioids should be considered for children where severe pain is anticipated, provided respiratory rates and levels of sedations are monitored.[66]

- **NSAIDs:** whilst ketorolac is not indicated or recommended for use in children,[48] IV ketorolac is used widely in paediatric postoperative pain with the ability to reduce opioid use.[67,68] In children aged >2 years IV ketorolac 0.5–1 mg/kg can be administered by bolus infusion over no less than 15 seconds.[48] IV dosing of ketorolac may be repeated every six hours up to 48 hours. SL ketorolac has demonstrated comparable efficacy to tramadol in severe acute pain in children.[69] SL dosing is not licensed for use in children in Europe but is used off-label. Use of combination NSAIDs e.g. ibuprofen and diclofenac or ketorolac is not advised.
- **Paracetamol:** available in oral suspension 120 mg/5 ml and should be dosed by patient bodyweight up to 4 times daily.[54] It should be used with care in patients with renal or hepatic impairment.[54] Paracetamol suppositories (60, 125, 250 mg) are also available and should be dosed by age i.e. one 60 mg suppository for children aged ≤1 year; one 125 mg suppository for those aged 1–5 years; one 250 mg suppository for those aged >6 years and two 250 mg suppositories for those aged >12 years.[55] The doses may be repeated to a maximum of 4 times in 24 hours.[55]

Other considerations for achieving analgesia in children

- **Ondansetron:** in cases of opioid-induced nausea and vomiting it is recommended to use an anti-emetic such as ondansetron. Administer as a single dose based on 0.15 mg/kg by slow IV (over 30 seconds) or SL 0.1–0.2 mg/kg to a maximum dose of 8 mg.[75]

Dosing cautions and contraindications

- **Codeine:** a recent clinical practice guideline recommendation reiterates current EMA guidance that codeine should NOT be prescribed in patients <12 years, or adolescents aged 12–18 years who have obesity, obstructive sleep apnoea or severe lung disease.[16,63] Codeine is contraindicated in patients with liver disease and patients at risk of increased intracranial pressure. Codeine must not be used in patients known or suspected of being CYPD26 ultra-rapid metabolisers (1%–2% of the population) owing to the high risk of toxicity.[14,76] Use with caution at reduced doses in patients with asthma or decreased respiratory reserve and avoid use in patients with renal or hepatic impairment.[76]
- **Ketamine:** contraindicated for use in patients where an increase in blood pressure would be hazardous, but consider the risk/benefits i.e. would an increase in blood pressure due to pain be more problematic than blood pressure increases due to ketamine.[25] Consider dose reductions in patients with hepatic impairment.[25]
- **Nitrous oxide/oxygen:** contraindicated for use in patients with head injuries or impaired consciousness, pneumothorax, air embolism, otitis media, suspicion or evidence of decompression sickness, severe bullous emphysema, gross abdominal distension, and patients with maxillofacial injuries.[43,77]
- **NSAIDs:** contraindicated in patients with active or previous GI ulcers, and patients with severe hepatic or renal failure.[47] They are cautioned or contraindicated in patients with asthma, depending on their previous history of NSAID use. Diclofenac is contraindicated in children <14 years of age.[47] Ketorolac is used off-label only/ in children <16 years of age.[48] Use of combination NSAIDs e.g. ibuprofen and diclofenac or ketorolac is not advised.
- **Opioids:** morphine, fentanyl, sufentanil etc. are all associated with potential for life-threatening or fatal respiratory depression and patients need to be monitored during use. All opioids carry a risk of addiction, abuse and misuse and should be used at the lowest dose possible, for the shortest time, with post-discharge opioid prescriptions limited to 2–3 days only. Opioids should be used with caution in those with renal or hepatic impairment.[20,35,57] Do not use opioids in combination with other opioids.

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